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The Effects of Cortisone and Adrenocorticotropic Hormone (ACTH) on Certain Rheumatic Diseases

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SUMMARY

The adrenal cortical hormone, cortisone, and the pituitary adrenocorticotropic hormone (ACTH) possess potent antirheumatic properties. Their administration produces strikingly beneficial effects on a number of rheumatic diseases including rheumatoid arthritis, rheumatoid (ankylosing) spondylitis, acute rheumatic fever, disseminated lupus erythematosus, periarteritis nodosa, psoriatic arthritis, dermatomyositis, and gout. In general the effects of these substances are temporary and they cause suppression rather than cure of the disease processes. Improvement is maintained usually only by continuing administration, and on hormonal withdrawal prompt or fairly prompt relapse of the disease manifestations ensues. In addition to their antirheumatic effects cortisone and ACTH influence a wide variety of physiologic functions. Administration of them therefore may produce a number of metabolic and clinical changes, some of which are not advantageous from a therapeutic standpoint. Adverse side-reactions are more liable to occur when large doses of the hormones are given for prolonged periods; such reactions appear to be reversible and disappear when administration of the hormones is stopped. With cortisone, comparatively few untoward signs develop when smaller amounts are administered continuously even for periods of months.

Greater clinical experience is needed before optimal doses and schedules of administration are finally determined. It appears that some severe cases, many moderately severe cases, and most moderate and mild cases of rheumatoid arthritis may be adequately controlled with smaller "maintenance" doses of cortisone ranging from 32 to 65 mg. a day, providing larger doses to suppress the disease manifestations are employed initially.

Neither cortisone nor ACTH should be considered as a therapeutic agent for general use until more information regarding their physiologic activities and the consequences of prolonged or repeated administration of them are available. Until the potential dangers of these hormones can be determined precisely, the use of them should be considered as an investigative procedure.

ALTHOUGH some rheumatologists have suspected that certain rheumatic diseases might be influenced by the function of the endocrine glands, no direct clinical or experimental evidence was available to support this consideration. Their ideas remained poorly defined until recently when Hench, Kendall, Slocumb and Polley, and subsequently others, demonstrated that the adrenal cortical hormone, cortisone (Compound E), and the adrenocorticotropic hormone from the anterior pituitary gland, ACTH, exert strikingly beneficial effects on a number of rheumatic diseases.

That cortisone and ACTH possess potent anti-

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rheumatic properties was not a chance discovery. The trial of these substances in patients with rheumatoid arthritis and allied diseases was prompted by deductions drawn from clinical observations. Rheumatoid arthritis is capable of spontaneous regression and not infrequently the course of the disease may be interrupted by spontaneous remissions, partial or complete, temporary or permanent. The disease, therefore, has the inherent capacity of spontaneous reversibility although this potentiality often remains dormant.[19] Certain procedures heretofore considered to be unrelated in their modes of action are known to stimulate, although feebly, the potential reversibility of rheumatoid arthritis and thereby to induce temporary amelioration of the disease. These procedures include febrile reactions from foreign proteins, starvation, surgical procedures, and surgical anesthesias. Much more potent and more regular antagonists of rheumatoid arthritis are pregnancy and jaundice from biliary obstruction or hepatitis.[16, 17] Although the relief from these various procedures and states appeared to be produced in diverse and unrelated ways, Hench speculated that a common mechanism might exist. Further, he was unable to reconcile the microbic theory of etiology with the powerful ameliorative influence of jaundice and pregnancy, states which are not known to influence favorably the course of proved bacterial or viral infections. If the agent which produced articular relief in jaundice were closely related or identical to the agent responsible for relief in pregnancy, Hench reasoned that the responsible substance must be common to both sexes and that it was not a unisexual factor. He conjectured that a bisexual hormone, possibly a hormone from the adrenal cortex, might be involved in the curious antirheumatic effect of pregnancy and jaundice.

In September 1948, Hench, Kendall, Slocumb and Polley administered cortisone to a patient with severe rheumatoid arthritis; striking and rapid improvement in the clinical and laboratory features of the disease resulted. In April 1949 these investigators reported dramatically favorable effects on severe or moderately severe rheumatoid arthritis from cortisone in 14 patients and from ACTH in two patients.[20] Subsequently cortisone and/or ACTH have been found to be beneficial in other rheumatic diseases, including to date acute rheumatic fever, rheumatoid (ankylosing) spondylitis, disseminated lupus erythematosus, periarteritis nodosa, psoriatic arthritis, dermatomyositis, and gout.

Certain experiments in animals also suggested that adrenocortical function may be related to rheumatic disease. In 1944 Selye and his co-workers observed that rats with intact adrenal glands occasionally developed joint lesions, similar histologically to the articular changes of rheumatic fever, when large doses of desoxycorticosterone were given.[41] The arthritis was transient, tending to disappear within a few weeks in spite of continued administration, and it developed in only a small percentage of the rats so treated. Other alterations of a "rheumatic type," such as arteritis simulating periarteritis nodosa, myocarditis with Aschoff body formation and encephalitis, occurred more regularly. When overdoses of desoxycorticosterone were given to adrenalectomized rats, the joint manifestations developed more frequently and the extra-articular changes were more pronounced. Since the discovery that cortisone and ACTH favorably influence certain rheumatic diseases, Selye attempted to explain this observation:[40] The action of desoxycorticosterone may be antagonized by glucocorticoids (cortisone-like steroids. Adrenalectomy may sensitize the animal to the toxic effects of desoxycorticosterone by removing the endogenous source of glucocorticoids. Thus in adrenalectomized animals rheumatic lesions are produced more frequently with overdoses of desoxycorticosterone.

Recently Selye reported observations on the influence of anterior pituitary and adrenal cortical hormones on experimentally induced non-specific chemical arthritis.[40] By injecting dilute solutions of formaldehyde in the hind paw of animals, acute arthritis and periarthritis were produced in the adjacent joints. When large or repeated doses of formaldehyde were injected, chronic arthritis and periarthritis developed; these were self-maintaining proliferative changes which continued for weeks after the irritant was discontinued, and microscopically the lesions resembled those found in the "chronic stage of rheumatoid arthritis." The arthritis was intensified if the rats were given either desoxycorticosterone or crude lyophilized anterior pituitary extract for several days beforehand. Conversely, pretreatment with either cortisone or ACTH almost completely inhibited the development of "formalin arthritis." Furthermore, experimentally produced alarm reactions (forced exercise, exposure to cold, spinal cord transection, starvation) inhibited the development of articular reactions from formaldehyde. The preventive effect of severe stress was interpreted as due to increased endogenous secretion of ACTH and hence of glucocorticoids. Adrenalectomized animals subjected to similar stresses were not so protected. Deductions were drawn that the inhibitory actions of ACTH, cortisone, and alarm reactions were due to the direct effect of cortisone-like glucocorticoids upon the injured tissues. Selye suggested that the antiarthritic effects of ACTH and cortisone are probably non-specific in nature rather than disease-specific.

The known hormones derived from the adrenal cortex may be classified broadly according to their principal functions as follows: (1) electrolyte regulating steroids; (2) carbohydrate regulating steroids (glucocorticoids), and (3) sex-like steroids (principally androgenic). Cortisone (Compound E) belongs to the group of carbohydrate-regulating hormones, along with Compounds A (11-dehydrocorticosterone), B (corticosterone), and F (17-hydroxycorticosterone). Cortisone and Compound F are the most active of the carbohydrate-regulating hormones derived from the adrenal cortex.

In 1946 Sarett at the Merck Laboratories, working in cooperation with Kendall and his colleagues at the Mayo Clinic, accomplished partial synthesis of cortisone from a bile acid (desoxycholic acid).[24] The product, although still scarce and expensive, is now being produced synthetically in sufficient quantity to allow limited clinical evaluation.

From 1936, when Kendall and his colleagues first isolated the hormone from extracts of the adrenal cortex,[25, 31] until its synthetic production in 1946, only minute quantities of cortisone were available for research in animals. Yet, in spite of its scarcity, important facts regarding its physiologic activities were determined, some of which may be summarized as follows: Cortisone (1) influences carbohydrate and protein metabolism, inducing (under certain experimental circumstances) hyperglycemia, glycosuria, and negative nitrogen balance; (2) affects the metabolism of electrolytes (although relatively feebly); (3) maintains life in adrenalectomized animals; (4) produces lysis of lymphocytes and eosinophils; (5) increases the resistance of adrenalectomized animals to the various stresses; (6) depresses adrenal cortical function with resulting decrease in 17-ketosteroid excretion; (7) produces atrophy of the adrenal and thymus glands, lymph nodes, and spleen; (8) increases antihyaluronidase activity; (9) increases the muscle work capacity of adrenalectomized animals; (10) produces regression of certain malignant mouse tumors.

Adrenal cortical function is regulated mainly by the function of the anterior pituitary gland through the medium of its adrenocorticotropic hormone (ACTH). ACTH, a complex protein substance with a molecular weight of nearly 20,000, was isolated in pure form in 1943 by Li and collaborators[27] and by Sayers and co-workers.[39] More recently Li has demonstrated that the active adrenocorticotropic principle is contained in a less complex peptide fraction of ACTH.[26, 28] Supplies of the hormone are dependent upon extraction from animal pituitary gland tissue, and because of its protein structure the prospects for its synthesis in the near future are remote. Although scarce, the supply of ACTH has been sufficient to allow fairly extensive experimentation in animals and limited clinical trials in human subjects.

The administration of ACTH to animals and humans with responsive adrenal glands results in increased secretion of glucocorticoids, some of which are closely allied to cortisone, and also in increased secretion of other cortical hormones such as those which influence electrolyte metabolism and androgenic function. Thus the administration of ACTH produces in general the following results: (1) affects carbohydrate and protein metabolism (inducing hyperglycemia, glycosuria, and negative nitrogen balance); (2) alters electrolyte metabolism, causing increased excretion of potassium and decreased excretion of sodium; (3) reduces the alkaline phosphatase content of plasma; (4) promotes hematologic changes which include reduction in total eosinophil and lymphocyte counts, increase in circulating neutrophils, and atrophy of lymph nodes; (5) causes prompt and greatly increased excretion of both 11-oxysteroids and 17-ketosteroids; (6) enhances the excretion of uric acid; and (7) augments antihyaluronidase activity. In patients with Addison's disease or in adrenalectomized animals these effects are not provoked. When ACTH is given to animals adrenal cortical hypertrophy may result[36] and the cholesterol and ascorbic acid contents of the gland are quickly reduced.[37, 8, 38] The depletion of cholesterol suggests that this substance may be utilized in the formation of steroid hormones.[11] The relationship between ascorbic acid and the cortical steroids is not definitely established but the gland's sensitive ascorbic acid response is used as a means of bioassaying the potency of ACTH.

INFLUENCE OF CORTISONE AND ACTH ON RHEUMATIC DISEASE

It has been estimated that in America up to January 1, 1950, approximately 160 patients with rheumatic disease had been given cortisone and about 175 had received ACTH.[13] The data included herein are based upon studies (some still unpublished) which have been made on many of these patients, and also upon personal experiences with 62 rheumatic patients to whom the author has administered cortisone.

RHEUMATOID ARTHRITIS

The dramatic response of rheumatoid arthritis to cortisone and ACTH, as first described by Hench, Kendall, Slocumb and Polley, has now been confirmed by several investigators.[4] The experiences have been practically uniform and each group of observers has found that patients with the disease in its various manifestations improved promptly and greatly with administration of the hormones. All observers have agreed that while these substances exert a pronounced suppressive effect, their influence is not curative but temporary, and in most instances exacerbations of the disease result when administration of the hormones is stopped. Hench and co-workers[21] recently reported their general results in 23 patients with rheumatoid arthritis who received cortisone or ACTH, or both, in large doses for total periods ranging from 11 to 218 days. The antirheumatic response was 90 to 95 per cent relief of disability in 14 patients, 75 to 90 per cent relief in eight patients, and moderate relief in one patient.

Response of Articular Manifestations to Cortisone and ACTH

A fairly definite pattern of improvement is noted with cortisone administration. Within a few days (or hours in some cases) there is pronounced reduction in stiffness of muscles and joints, lessening of articular aching, tenderness, and pain on motion, and significant improvement of articular and muscular function. Usually the first symptoms to subside are muscular and articular stiffness and rest pain, and within one to four days the patients may have no further desire for acetylsalicylic acid or

other analgesics. Next in order of improvement are lessening of joint pain on motion, increased motion and decreased tenderness of the joints. Reductions in articular swellings are usually slower in appearing and may not be complete, but sometimes swellings and effusions recede rapidly and completely. Within seven to ten days mild flexion deformities may be corrected. In spite of advanced muscle atrophy and previously restricted joint motion, muscle strength and joint function may return to a remarkable degree within a few days. In early and less severe cases, complete remissions may ensue with disappearance of all abnormal physical signs. In severe cases and in cases of longer standing, some articular swelling and effusion, together with some tenderness, may persist even when relatively large doses of the hormone are given for prolonged periods. Destructive changes in cartilage and bone, fixed deformities, and ligamentous calcification are not changed. Non-articular features, such as subcutaneous nodules, enlarged lymph nodes, bursitis, and tenovaginitis improve or disappear along with the improvement in the joints.

Prompt and significant improvement in the musculoskeletal manifestations, similar qualitatively to that resulting from cortisone, occurs with the administration of ACTH in adequate doses.* Striking reductions in stiffness, pain, articular tenderness and swelling are noted within a few days. As with cortisone, the beneficial effects are usually temporary and the manifestations of the disease revert to their original intensities, often promptly, after withdrawal of the hormone.

Influence on Constitutional Symptoms

A definite sense of well-being is exhibited by most patients during administration of cortisone or ACTH, the degree of mental stimulation varying somewhat with the size of the daily dose given. Some patients who are initially depressed and pessimistic become frankly euphoric. Because the psychologic response is often greater than would be anticipated merely from pain relief and improvement in the physical condition, it appears that these hormones may have a positive euphoristic action. Other effects on constitutional symptoms include: Loss of "toxic feeling," increased general strength and endurance, and change in libido (increase in some, decrease in others) in males. Patients who are febrile usually become afebrile within 24 to 72 hours and remain so during the period of administration. Appetites tend to improve rapidly and corresponding increases in food consumption, general nutrition, and body weight are noted. Such weight gains as 19 pounds in 40 days, 21 pounds in 60 days, 26 pounds in 60 days, and 41 pounds in 218 days have been recorded.[20, 21, 7]

Influence on Laboratory Tests

Erythrocyte sedimentation rates: Significant decreases in the erythrocyte sedimentation rate occur usually within a few days after cortisone or ACTH administration is started; the decreases occur promptly and rapidly in some patients, more slowly in others. With cortisone in daily doses of 100 mg., the rates ordinarily decrease at a speed of about 2 to 4 mm. per hour from one day to the next, but in some the correction is more rapid, proceeding with a daily average reduction of 4 to 7 mm. per hour;[20] frequently rates become normal within ten to 35 days. With short-term administration of cortisone, decreases varying from 15 to 75 mm. may be noted within periods of eight days.[6] Even more prompt and more steady decreases in rates may result from the administration of large doses of ACTH.[20, 21]

Erythrocyte counts and hemoglobin determinations: When anemia is present, erythrocyte counts may increase by 500,000 to 1,000,000 cells per cu. mm., and hemoglobin determinations may increase by 1.4 to 2.0 gm. per 100 cc. within a few weeks.[20] Even with short-term administration, pronounced improvement in the erythrocyte count and hemoglobin value may be noted.[6]

Leukocyte counts: Small, but significant, increases in the total number of circulating leukocytes may be noted during prolonged administration of cortisone. Consistent changes in the number of lymphocytes or eosinophils usually do not occur.[43, 21] When ACTH is given in doses of 100 mg. daily, complete or almost complete disappearance of circulating eosinophils usually results.[45]

Articular biopsies: When performed after several weeks of cortisone or ACTH administration, articular biopsies reveal definite reductions of synovial inflammation, but the synovial tissues are still not normal. Microscopic findings include a decreased number of plasma cells and lymphocytes, reduction of papillary tufting, reduced deposition of fibrin, and lessened necrosis and edema.[20, 21]

Electrocardiograms: Except for slowing of the heart rate, no significant changes are noted as the result of cortisone administration.[6]

Electroencephalograms: Changes in the electroencephalographic pattern have been observed with both cortisone and ACTH administration,[6, 32] but the full significance of these alterations has not yet been reported.

Corticosteroid excretion:[43, 20] Urinary concentrations of corticosteroids are increased initially when large doses (100 to 200 mg.) of cortisone are given. With continued administration of 100 mg. daily, the amount excreted may remain elevated or decline toward control values. The increased urinary concentrations probably represent the excretion of unchanged cortisone (a corticosteroid) and metabolites of cortisone which give the same chemical reactions as corticosteroids.[21] ACTH promotes prompt and pronounced increased corticosteroid excretion. Thirty to 50 per cent of the total amount excreted consists of Compound F (17-hydroxycorticosterone), indicating that ACTH may stimulate the adrenal cortex to form Compound F rather than cortisone.

*See References 20, 13, 42, 30, 23, 3, 32.

17-ketosteroid excretion:[43, 20, 21] When cortisone is given in daily doses of 100 mg., the daily excretion of 17-ketosteroids is reduced at first and later increased, but it remains less than the pre-cortisone level for as long as cortisone is given and for some time thereafter. When the daily dose is increased from 100 mg. to 200 mg., the excretion of 17-ketosteroids increases sharply and may surpass the pre-cortisone amounts. Hench, Kendall, Slocumb and Polley[21] make the following interpretation: The administration of cortisone promptly depresses adrenal cortical function so that the cortex produces smaller amounts of those steroids (among them cortisone) which are precursors of 17-ketosteroids—thus the excretion falls. But the catabolism of injected cortisone involves the production of small amounts of 17-ketosteroids—hence after an initial fall the total daily excretion increases somewhat. With very large doses (200 mg. daily) of cortisone, the amount of injected material which is catabolized to 17-ketosteroids may more than compensate for the suppressed function of the adrenal cortex.

Administration of ACTH stimulates adrenal cortical function and causes pronounced increases in 17-ketosteroid excretion.

Plasma electrolytes:[43, 32] Cortisone given in doses of 100 mg. daily does not cause significant alterations in the balance for sodium, potassium, and chloride, or in the concentrations of electrolytes in the extracellular fluid. But with daily doses of 200 mg. cortisone regularly induces a negative balance for potassium. The long range effects of such large doses on excretion of sodium and chloride are variable; the most common are retention of these ions early, followed later by increased excretion. ACTH in doses of 100 mg. daily produces a negative balance for potassium. At first there is marked retention of sodium and chloride, then later these ions may be excreted in increased amounts.

Urinary total nitrogen: [43, 32] Nitrogen excretion is not changed significantly when the dose of cortisone is 100 mg. daily, but it is decidedly increased when the dose is 200 mg. daily. A negative nitrogen balance occurs during ACTH administration in large doses (100 mg.) but nitrogen excretion may fall to control levels when the daily dose is lowered.

Uric acid in serum and urine:[43, 32] Uric acid excretion is only slightly increased with the administration of 100 mg. of cortisone daily. The excretion is moderately increased with ACTH in daily doses of 100 mg. Significant decreases in serum uric acid occur most commonly with ACTH or cortisone when initial serum uric acid levels are in the upper normal range or above normal.

Carbohydrate tolerance:[32, 6, 43, 21] Slight inconstant increases in the fasting blood sugar have been observed in some cases during administration of cortisone or ACTH, but rarely have the values exceeded normal. In most cases glucose tolerance tests are not altered conspicuously during cortisone administration although several patients have shown slightly decreased tolerances. The tolerance was reduced sufficiently to produce diabetic curves in two cases studied by the author. Yet with continued administration of cortisone neither glycosuria nor clinical evidence of diabetes developed. In normal subjects given large doses of ACTH, some investigators have found that a temporary state of metabolism similar to that of diabetes mellitus could be caused;[10, 9] impairments of carbohydrate tolerance so induced have been reversible and have disappeared after withdrawal of the hormone.

Serum proteins:[43, 32, 20, 21] The effect of cortisone and ACTH is to increase serum albumin and decrease serum globulin if the pretreatment values of these substances are abnormal.

Sensitized sheep cell agglutination:[32] This reaction remained positive in seven of eight patients treated with ACTH; in one patient a positive agglutination changed to a doubtful reaction.

Course After Discontinuance of Cortisone and ACTH

In most instances clinical improvement is sustained only by continuing administration, and cessation of the hormones results, as a rule, in prompt or fairly prompt relapse of the disease. In eight of nine cases reported by Hench, Kendall, Slocumb and Polley[20] in which cortisone was discontinued after short-term administration, the symptoms and signs began to return within two to four days after withdrawal of the compound; the return progressed slowly in six cases and rapidly in two. In the remaining one case most of the improvement was retained five months after the drug was stopped. In seven of eight cases observed by Boland and Headley[6] relapse occurred on withdrawal of the medication, and within four weeks the clinical and laboratory manifestations had returned to their original intensities; in one case 75 per cent of the initial improvement was retained. As with cortisone, withdrawal of ACTH is usually followed by rapid return of symptoms.[20, 32, 45, 35, 13, 23]

Adverse Physiologic Effects Induced by Cortisone and ACTH

Cortisone and ACTH are potent hormones which are capable of influencing a wide variety of physiologic functions. While they exert strikingly beneficial action on certain rheumatic and other diseases, undesirable metabolic and clinical signs of adrenocortical hyperfunction may attend their use. In varying combinations these adverse effects have included:[21, 7, 43, 20, 5] (1) signs of altered fluid balance such as edema, sudden gains in weight, polydipsia and oliguria; (2) rounding of the facial contour, probably due to localized deposition of adipose tissue; (3) signs of increased androgen activity such as acne and mild hirsutism; (4) changes in libido, potentia, and menstruation (irregular menses or amenorrhea); (5) nervous system effects such as euphoria, nervousness, insomnia, changes in mood or psyche, paresthesias, and func-

tional symptoms of psychoneurosis; (6) cutaneous striae; (7) weakness, fatigue and exhaustion; (8) impaired carbohydrate tolerance; (9) alkalosis with lowered blood potassium levels; (10) miscellaneous effects such as transient headaches, dizziness or light-headedness, transient blurring of vision, thinning of the hair, and pigmentation of the skin (especially of the face and neck).

Adverse side-effects are usually mild, are reversible, and disappear when administration of the hormones is stopped. They are commonly encountered when large doses (100 mg. daily or more) are given for long or fairly long periods. Of 23 patients studied by Hench and associates,[21] most of whom received large doses of cortisone or ACTH for long periods, side-effects developed in 14 (61 per cent). They were mild in eight (35 per cent), moderate in two (9 per cent), and pronounced in four (17 per cent). Of nine patients treated by Bauer with large doses of cortisone (100 to 150 mg. daily for eight to 12 days) and ACTH (75 to 200 mg. daily for 12 days to four months), undesirable side-reactions were observed in "almost all patients."[13] Freyberg[14] noted no serious complications with 17 patients who received cortisone or with 16 who received ACTH, and some were treated for periods as long as 160, 150, 145, and 120 days. Untoward changes are more liable to occur in females than in males, presumably because of their more complex hormonal mechanisms.[7, 21, 13]

Whereas individual tolerance may play some role in the development of side-effects, the chief factors appear to be dosage and length of administration. In the author's experience with cortisone, adverse signs have been noted usually in those patients receiving large doses (such as 100 mg. or more daily). In an attempt to avert or minimize the development of hypercortisonism it has been the author's practice to give initial large doses only for a period long enough to produce satisfactory suppression of the disease. The dosage is then gradually reduced until the smallest daily amount is reached which will sustain adequate control. When the rheumatic manifestations can be controlled with maintenance doses averaging 32 to 65 mg. daily, comparatively few side-effects of the hormone have been encountered. Although such smaller doses have been continued with but few untoward reactions for more than four months in a number of patients, it is possible that undesirable signs might develop after more prolonged administration.

Signs of hormonal excess from cortisone or ACTH have been sufficient in several cases to produce clinical pictures of Cushing's syndrome. Hench, Kendall, Slocumb and Polley described one such case in their first report.[20] The patient was a 29-year-old female who, after receiving cortisone in daily doses of 100 mg. for a period of six months, developed acne, mild hirsutism, moon-like face, amenorrhea, mental depression, and impaired carbohydrate tolerance. The manifestations were temporary, however, and disappeared when the hormone was discontinued.

Decreases in carbohydrate tolerance, as measured by glucose tolerance tests performed before and during administration of cortisone, have been observed in a few patients;[6] but in most instances no significant changes have been found even after prolonged administration of large doses (100 mg. daily). In two patients with initially normal curves observed by the author, the tolerance decreased during administration to the extent that diabetic types of curves developed.[7] Administration of cortisone was continued in both patients, and their usual diets were maintained; yet in neither have glycosuria or clinical signs of diabetes appeared. More striking changes in carbohydrate tolerance might be expected if the hormone were administered to individuals having latent or frank diabetes mellitus. One of the first patients treated by the author had coexisting diabetes mellitus and rheumatoid arthritis, and the diabetes was temporarily intensified during the administration of cortisone (200 mg. daily for two days, then 100 mg. daily for six more days.)[6] The daily insulin requirement before cortisone was 10 units and during the use of cortisone was between 30 and 50 units while the patient remained on a constant measured diet. Three days after withdrawal of the hormone the insulin requirement reverted to the pre-cortisone amount of 10 units.

The potential dangers from the use of either cortisone or ACTH cannot yet be fully appraised and further studies are needed before the limitations of prolonged administration can be assessed. Some observers have expressed apprehension that administration of these hormones for periods of months or years might result in persistent adrenal cortical hyperplasia from ACTH on the one hand, and persistent atrophy from cortisone on the other;[22] but so far all adverse effects have been temporary, have disappeared on hormonal withdrawal, and no evidence for permanent damage has been offered. Until the dangers can be determined precisely, however, the use of these hormones should be considered as an investigative rather than a therapeutic procedure.

Dosage and Schedule of Administration of Cortisone and ACTH

Greater clinical experience with these hormones and more knowledge about their physiologic activities and more information regarding the consequences of their prolonged or repeated administration are needed before optimal dosages and best schedule of administration can be determined. Milligram for milligram, cortisone and ACTH do not have physiologic equality.[21] Approximately one-half as many milligrams of ACTH as cortisone are needed to produce the same clinical effect, or in other words 100 mg. of ACTH stimulate the adrenal cortices to produce about 200 mg. of cortisone-like steroids. Because ACTH is rapidly absorbed and utilized, the best results are obtained by giving the total dose in divided doses two to four times daily. Cortisone is absorbed more slowly and one injection

a day (or every second day in some cases) is sufficient.

To accomplish remissions in adults with severe or moderately severe rheumatoid arthritis Hench, Kendall, Slocumb and Polley found that daily doses of 100 mg. of cortisone acetate were required.[20] Most of their patients were given 300 mg. on the first day and thereafter 100 mg. daily. Doses of 75 mg. daily were usually less than completely effective in severe cases, and smaller doses of 25 or 50 mg. were inadequate or totally ineffective. Of ACTH they generally gave 100 mg. daily but in some cases the daily dose varied from 45 to 140 mg.[21] Other observers have obtained good results with daily doses of ACTH ranging from 20 to 100 mg.[45,32,35,23] In Holbrook's experience[23] ACTH in total daily doses of 40 mg. was usually effective, while Ragan and colleagues[32] held two patients under satisfactory control with doses of 10 or 15 mg. given twice daily.

In an attempt to avert undesirable side-effects various schedules have been tried. Hench and coworkers[21] have suggested that interrupted administration or a "course method" might provide a more physiologic response than would continuous administration to the limits of individual tolerance. A few of their patients who were treated intermittently, or with intermittent but alternating courses of ACTH and cortisone, have experienced temporary secondary rebound remissions. In other words, on withdrawal of either cortisone or ACTH an initial short relapse occurred which was then followed by a second remission. This suggested to them that remissions resembling spontaneous ones might be produced in some cases by interrupted therapy.

The author, too, has tried to find a method which would eliminate or minimize adverse effects and yet preserve therapeutic effectiveness. With cortisone it has been possible to maintain improvement with smaller doses in the majority of patients with rheumatoid arthritis providing the disease manifestations have first been suppressed with larger doses given initially. With continued administration of smaller daily maintenance doses, control of the manifestations has usually been adequate although not always as complete as with larger daily doses. But it is probably more prudent to control patients adequately with smaller doses than to attempt to obtain complete or absolute results with large and probably unsafe amounts of the hormone.

The procedure followed by the author in severe and moderately severe cases is, at present, to give 200 mg. of cortisone on the first day and then 100 mg. daily thereafter until the clinical manifestations have improved satisfactorily and the erythrocyte sedimentation rate has reached, or is approaching, a normal value. The time required for this result varies widely from two to six weeks. The dose is then gradually lowered in step-wise fashion until the smallest dose is found which will control the clinical manifestations. If significant side-effects occur during the initial period when larger doses are being given, the dosage is reduced sooner. Some severe and many moderately severe cases have been controlled adequately on daily doses averaging from 50 to 65 mg. For mild and moderate cases the same procedure is adhered to except that only 100 mg. is given on the first day; the time needed to suppress the disease is usually shorter than with severe cases and dosage can be decreased earlier. Most mild and moderate cases have been controlled adequately, some completely or almost completely, with doses averaging 32 to 50 mg. per day. Doses of 100 mg. given every other day appear to be as effective as doses of 50 mg. given daily. Many patients have been maintained satisfactorily with doses of 100 mg. given three times a week. Details of these observations will be published elsewhere.[7]

JUVENILE RHEUMATOID ARTHRITIS (STILL'S DISEASE)

Juvenile rheumatoid arthritis responds in the same way as the adult form to cortisone and ACTH.[13,23,12,35] The details of two cases were reported by Elkinton and collaborators.[12] A five-year-old boy, treated with 25 mg. of ACTH daily for seven days, became afebrile within 12 hours, and within 48 hours the painful joint swellings had subsided for the most part. A nine-year-old girl, given ACTH intermittently and in varying doses over a period of 152 days, demonstrated dramatic clinical improvement during each period of administration, but with daily doses of 50 to 60 mg., signs of hyperadrenalism developed. Adequate dosage of these hormones in children apparently depends more on the severity of the disease than on body size. As much may be needed for adequate antirheumatic response as in an adult, but the metabolic and endocrine complications may be greater in the child because of the larger ratio betwen hormone dose and body size.[13]

RHEUMATOID (ANKYLOSING) SPONDYLITIS

Results similar to those obtained in peripheral rheumatoid arthritis have been produced by cortisone and ACTH in patients with typical rheumatoid (ankylosing) spondylitis. Temporary remissions were provoked in each of six patients treated by Freyberg with cortisone.[13] Holbrook gave ACTH in doses of 40 mg. daily for ten to fourteen days to four spondylitic patients and each was decidedly improved.[23] One patient retained 75 per cent of the improvement for three months, whereas exacerbations occurred promptly in the remaining three patients when the hormone was discontinued.

RHEUMATOID ARTHRITIS WITH PSORIASIS

A few patients with rheumatoid arthritis and coexisting psoriasis have been given ACTH or cortisone. The articular response has not differed from that observed in uncomplicated rheumatoid arthritis, and in each instance there has been concomitant improvement in the psoriatic skin lesions.[18, 23, 35, 7] A patient with severe psoriasis and moderately severe psoriatic arthritis was treated with cortisone (100 mg. daily for 43 days) and later with ACTH (3.5 gm. within 28 days).[21] During each course the

arthritis disappeared promptly, but the psoriasis improved slowly: "Remissions, not cures, were induced."

ACUTE RHEUMATIC FEVER

The favorable influence of cortisone and ACTH on acute rheumatic fever has been reported by several investigators. The group at the Mayo Clinic[21,2,1] has given cortisone during the acute phase of the disease to seven patients and ACTH to four others. The doses of cortisone were 200 mg. for the first few days, then 100 mg. daily. Total doses of 3.45 to 5.2 gm. were given for periods of 22 to 40 days. Initial doses of ACTH were 25 to 60 mg., then later 10 to 15 mg. daily, with total doses of 400 to 825 mg. within 16 to 38 days. Rapid disappearance not only of fever, tachycardia, and polyarthritis, but also of sedimentation rate acceleration and electrocardiographic abnormalities, resulted. Fever subsided within one to six days and the joints became symptom-free within two to eleven days. Sedimentation rates were refractory for the first two to five days and then decelerated rapidly; decreases as great as 100 mm. in one hour were noted within periods of 10 to 14 days and the rates in seven of the eight cases became normal within 20 days. Prolonged P-R intervals in five patients were restored to normal within one to eleven days. In three of the eight cases mild rheumatic recurrences appeared within two to six weeks, but these subsided when the hormones were given again and then did not reappear. Cardiac examinations made eight to ten months following the attacks revealed no evidence of new, or increased old, rheumatic carditis. Although no definite conclusions were drawn, it was hoped that rapid termination of the process with cortisone or ACTH might prevent or lessen the development of chronic sequelae in the heart valves and myocardium.[20] Thorn and collaborators[45] treated three patients with ACTH in doses of 40 mg. daily for periods ranging from eight to fourteen days; detailed results were not given but the response was said to be more striking than that obtained with ACTH in rheumatoid arthritis.

PERIARTERITIS NODOSA

Three patients with periarteritis nodosa were treated by Ragan and co-workers with ACTH, and in each there was subsidence of the activity.[32] Such manifestations as purpuric rashes, pruritus, asthma, periarteritic nodules and eosinophilia disappeared or were greatly reduced in severity, but recurred when the hormone was discontinued. A patient with histologically proved periarteritis nodosa was successfully treated with cortisone:[7] Periarteritic nodules, skin rash, joint swelling and tenderness disappeared, the erythrocyte sedimentation rate reverted to normal, and electrocardiographic changes were considerably reduced. After the disease was suppressed by daily doses of 100 mg., improvement was maintained by smaller daily doses of 40 to 50 mg.

DISSEMINATED LUPUS ERYTHEMATOSUS

Pronounced clinical improvement was noted in three patients with acute disseminated lupus erythematosus during the administration of ACTH in daily doses of 40 mg.[45] Two patients were treated with ACTH by Elkinton and associates.[12] One patient, given daily doses of 100 mg., became afebrile within 16 hours and the cutaneous lesions cleared within 14 days. Progressively smaller amounts of the drug were then given and finally after 51 days it was discontinued. The patient remained in "fairly complete remission" 60 days after the hormone was discontinued. The other patient had severe and apparently terminal disease with multiple visceral changes. Seventy-five to 160 mg. of ACTH was given daily, and striking improvement resulted, with fall in temperature, clearing of retinopathy, disappearance of pleural effusion, and diminution of the hepatosplenomegaly. The patient finally became refractory to the agent, however, and the manifestations returned after 44 days of treatment. Despite doses of 200 mg. daily, the patient died.

Hench and colleagues[21] gave cortisone or ACTH to six patients with severe disseminated lupus erythematosus. One patient received cortisone (usually 100 mg. daily) continuously for 166 days; arthritis, pericarditis, pleurisy, leukopenia, and "lupus erythematosus cells" in sternal bone marrow disappeared. The sedimentation rate decreased and the general condition improved greatly. When the hormone was discontinued mild relapse involving muscles and joints developed, but after six months much of the improvement was retained.

DERMATOMYOSITIS

A case of severe dermatomyositis in a five-year old boy was treated with three courses of ACTH.[12] After the first two courses, relapse occurred; but after the third and more prolonged course the disease had remained, at the time of the report, in complete remission for 117 days.

TUBERCULOUS ARTHRITIS

Hench and associates[21] tried the effect of cortisone on two patients with proved tuberculous monarthritis involving knee joints in order to determine what "non-specific" influence this hormone might have on joint disease of known bacterial origin. In one case the knee became essentially symptomless but pathologic and bacteriologic evidence of tuberculous arthritis persisted. On interruption of therapy the articular symptoms returned and a second course of cortisone again reduced the symptoms. The response in the other patient was similar. It was concluded tentatively that cortisone "controlled the hyperergic tissue reaction but did not exert a bacteriostatic or bactericidal effect."

OSTEOARTHRITIS

A patient with chronic lymphatic leukemia and coincidental, but symptomatic, primary osteoarthritis, involving especially the knees, was treated with cortisone.[21] Pronounced symptomatic improvement

in the articular symptoms resulted. One of the patients with peripheral rheumatoid arthritis treated by the author also had severe symptomatic osteoarthritis of the cervical spine. The administration of cortisone was accompanied by complete disappearance of aching and subjective stiffness of the neck, considerable reduction of pain on forced motion, but little or no lessening of restricted cervical motion. Another patient with moderately severe symptoms and roentgenographic evidence of severe osteoarthritis of the knees obtained neither subjective nor objective improvement from cortisone given in daily doses of 100 mg. for 21 days. Similarly, a patient with severe malum coxae senilis involving one hip obtained no relief.[7]

GOUT

Robinson and co-workers[33,34] found that when ACTH was given to normal non-gouty subjects there resulted a prompt increase in urate excretion which persisted throughout the injection period and reached a peak on the ninth day. However, there was no accompanying decrease in the blood urate values as determined by the uricase method. Similar results were observed by Thorn and co-workers,[44] who could not account for the increase on the basis of accelerated renal excretion alone, and postulated that the hormone must also increase urate production in normal subjects. ACTH administered to a patient with latent pretophaceous gout and hyperuricemia resulted in prompt increase in urinary urate excretion comparable in magnitude to that seen in normal subjects. In contrast to normal subjects, however, there was a concomitant fall in blood urate levels. Certain calculations led to the deduction that ACTH caused increased production of urates as well as increased clearance by the kidney.

When ACTH is given during an acute attack of gouty arthritis, prompt relief of the acute joint manifestations is produced.[15,46,34,29] A single dose of 50 mg., if given within eight hours of the onset, may suppress an attack for 24 hours or longer; relief usually occurs within a few hours of administration. However, when ACTH is withdrawn the attack usually recurs in the same or other joints. Colchicine given during, or immediately after, treatment of acute gouty arthritis with ACTH was found by some[46] to prevent a renewal of the attack upon withdrawal of ACTH.

Robinson, Conn, Block and Louis[33] and Hellman[15] gave ACTH to gouty patients during interval or latent periods between attacks, and then withdrew the hormone. On withdrawal most of the patients given more than 100 mg. of ACTH during a 24-hour period had an acute episode of gouty arthritis. The attack so provoked was relieved by further administration of ACTH, but again on withdrawal most patients had a renewed attack within a few days. This phenomenon was interpreted by Wolfson[46] as follows: With ACTH withdrawal an 11-oxysteroid lack is produced which precipitates acute gouty arthritis, while by administration of ACTH a state of 11-oxysteroid excess is produced which relieves the attack.

Administration of cortisone in large doses (200 to 300 mg.) produced prompt subsidence of objective and subjective manifestations in two patients with acute gouty arthritis;[7] relief occurred within five hours in one and within 18 hours in the other. As with ACTH, withdrawal resulted in acute recurrences of the attacks. In one case the recurrent episode was again suppressed by a second injection of 300 mg. of cortisone and the attack was terminated without further recurrence by giving progressively smaller daily doses over a period of eight days. In a patient with severe chronic tophaceous gouty arthritis joint tenderness, rest pain, and pain on weight-bearing disappeared within seven days with cortisone in daily doses of 100 mg.; improvement was maintained by giving 100 mg. three times a week, but no change resulted in the size of subcutaneous or osseous tophi even after four months of administration.

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REFERENCES

1. Barnes, A. R., and Smith, H. L.: Effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone: cortisone) and of pituitary adrenocorticotropic hormone (ACTH) on rheumatic fever, Indiana State M. J. In press.

2. Barnes, A. R., and Smith, H. L.: Effects of administration of cortisone and ACTH on patients with acute rheumatic fever, Mod. Concepts Cardiovas. Dis., Feb. 1950.

3. Bauer, W.: Personal communication.

4. Bauer, W., Boland, E. W., Freyberg, R. H., Holbrook, W. P., and Rosenberg, E. F.: Discussions, Proceedings Seventh International Congress on Rheumatic Diseases, May 30-June 3, 1949. In press.

5. Boland, E. W.: Relation of the adrenal cortex to rheumatic disease: A review of some recent investigations, Ann. Rheum. Dis., March 1950.

6. Boland, E. W., and Headley, N. E.: Effects of cortisone acetate on rheumatoid arthritis, J.A.M.A., 141:301-308, Oct. 1, 1949.

7. Boland, E. W., and Headley, N. E.: Unpublished data.

8. Carreyett, R. A., Golla, Y. M. L., and Reiss, M.: Action of gonadotropic hormone and of pituitary corticotropic hormone on cholesterol content of adrenals, J. Physiol., 104: 201-214, Oct. 15, 1945.

9. Conn, J. W., Louis, L. H., and Johnson, M. W.: Metabolism of uric acid, glutathione and nitrogen, and excretion of "11-oxysteroids" and 17-ketosteroids during induction of diabetes in man with pituitary adrenocorticotropic hormone, J. Lab. and Clin. Med., 34:255, Feb. 1949.

10. Conn, J. W., Louis, L. H., and Wheeler, C. E.: Production of temporary diabetes mellitus in man with pituitary adrenocorticotropic hormone; relation to uric acid metabolism, J. Lab. and Clin. Med., 33:651-661, June 1948.

11. Editorial, Some aspects of adrenal cortical function and pituitary-adrenal relationships, Ann. Int. Med., 31:925-931, Nov. 1949.

12. Elkinton, J. R., Hunt, A. D., Godfrey, L., McCrory, W. W., Rogerson, A. G., and Stokes, J.: Effects of pituitary adrenocorticotropic hormone (ACTH) therapy, J.A.M.A., 141:1273-1279, Dec. 31, 1949.

13. Freyberg, R. H.: Effects of cortisone and ACTH in rheumatoid arthritis (Panel discussion), Bull. New York Acad. Med. In press.

14. Freyberg, R. H.: Personal communication.

15. Hellman, L.: Production of acute gouty arthritis by adrenocorticotropin, Science, 109:280-281, March 18, 1949.

16. Hench, P. S.: Analgesia accompanying hepatitis and jaundice in cases of chronic arthritis, fibrositis and sciatic pain, Proc. Staff Meet., Mayo Clin., 8:430-436, July 12, 1933.

17. Hench, P. S.: Effect of jaundice on chronic infectious (atrophic) arthritis and on primary fibrositis: Further observations; attempts to reproduce the phenomenon, Arch. Int. Med., 61:451-480, March 1938.

18. Hench, P. S.: Personal communication.

19. Hench, P. S.: Potential reversibility of rheumatoid arthritis, Proc. Staff Meet., Mayo Clin., 24:167-178, March 30, 1949.

20. Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F.: Effect of a hormone of the adrenal cortex (17-hydroxy-11-dehydrocorticosterone: Compound E) and of pituitary adrenocorticotropic hormone on rheumatoid arthritis; preliminary report, Proc. Staff Meet., Mayo Clin., 24:181-197, April 13, 1949.

21. Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F.: Effects of cortisone acetate and pituitary ACTH on rheumatoid arthritis, rheumatic fever and certain other conditions: A study in clinical physiology, Arch. Int. Med., April 1950. In press.

22. Henly, A. A.: The adrenocorticotropic hormone, Annual Report, West London Hospital, Dept. of Rheumatic Diseases, pp. 18-26, 1949.

23. Holbrook, W. P.: Personal communication.

24. Kendall, E. C.: Some observations on the hormone of the adrenal cortex designated Compound E, Proc. Staff Meet. Mayo Clin., 24:298-301, May 25, 1949.

25. Kendall, E. C., Mason, H. L., Myers, C. S., and Allers, W. D.: Physiologic and chemical investigation of the suprarenal cortex, J. Biol. Chem., 114:57-58, May 1936 (in Soc. Proc.).

26. Li, C. H.: Chemistry of the hormones, Ann. Rev. Biochem., 16:291-322, 1947.

27. Li, C. H., Evans, H. M., and Simpson, M. E.: Adrenocorticotropic hormone, J. Biol. Chem., 149:413-424, Aug. 1943.

28. Luft, R., Sjögren, B., and Li, C. H.: Results of administration of adrenocorticotropically active peptides (ACTH peptides) to a patient suffering from rheumatoid arthritis, Acta endocrinol., 3:299, Dec. 1949.

29. Margolis, H. M., and Caplan, P. S.: Treatment of acute gouty arthritis with pituitary adrenocorticotropic hormone (ACTH), J.A.M.A., 142:256-258, Jan. 28, 1950.

30. Markson, D.E.: Prolonged treatment of rheumatoid arthritis with pituitary adrenocorticotropic hormone (ACTH), J.A.M.A., 141:458-459, Oct. 15, 1949.

31. Mason, H. L., Myers, C. S., and Kendall, E. C.: Chemical studies on the suprarenal cortex. II. The identification of a substance which possesses the qualitative action of cortin; its conversion into a diketone closely related to androstenedione, J. Biol. Chem., 116:267-276, Nov. 1936.

32. Ragan, C., Grokoest, A. W., and Boots, R. H.: Effect of adrenocorticotropic hormone (ACTH) on rheumatoid arthritis, Am. J. Med., 7:741, Dec. 1949.

33. Robinson, W. D., Conn, J. W., Block, W. D., and Louis, L. H.: Role of the adrenal cortex in urate metabolism and gout, J. Lab. & Clin. Med., 33:1473, Nov. 1948.

34. Robinson, W. D., Conn, J. W., Block, W. D., Louis, L. H., and Katz, J.: Role of the anterior pituitary and adrenal cortex in urate metabolism and in gout, Seventh Internat. Congress on Rheumatic Dis., May 30-June 3, 1949, New York.

35. Rosenberg, E. F.: Rheumatoid arthritis: Experiences with cortisone (Compound E), and other adrenal cortical steroids, and pituitary adrenocorticotropic hormone. To be published.

36. Sayers, G., and Sayers, M. A.: Regulation of pituitary adrenocorticotropic activity, Federation Proc., 5:200, March 1946.

37. Sayers, G., Sayers, M. A., Fry, E. G., White, A., and Long, C. N. H.: Effect of adrenotropic hormone of anterior pituitary on cholesterol content of adrenals with review of literature of adrenal cholesterol, Yale J. Biol. & Med., 16: 361-392, March 1944.

38. Sayers, G., Sayers, M. A., Liang, T. Y., and Long, C. N. H.: Effect of pituitary adrenotropic hormone in cholesterol and ascorbic acid content of adrenal of rat and guinea pig, Endocrinology, 38:1-9, Jan. 1946.

39. Sayers, G., White, A., and Long, C. N. H.: Preparation and properties of pituitary adrenotropic hormone, J. Biol. Chem., 149:425-436, Aug. 1943.

40. Selye, H.: Further studies concerning the participation of the adrenal cortex in the pathogenesis of arthritis, Brit. M. J., 4637:1129-1135, Nov. 19, 1949.

41. Selye, H., Sylvester, O., Hall, C. E., and Leblond, C. P.: Hormonal production of arthritis, J.A.M.A., 124:201-207, Jan. 22, 1944.

42. Spies, T. D., and Stone, R. E.: Relief of the symptoms of acute gout and rheumatoid arthritis by means of pituitary adrenocorticotropic hormone (ACTH), South. M. J., 42: 720, Aug. 1949.

43. Sprague, R. G., Powers, M. H., Mason, H. L., Albert, A., Mathieson, D. R., Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F.: Observations on the physiologic effects of 17-hydroxy-11-dehydrocorticosterone (cortisone) and adrenocorticotropic hormone (ACTH) in man, Arch. Int. Med., 85:199-258, Feb. 1950.

44. Thorn, G. W.: Quoted by Robinson et al.[34]

45. Thorn, G. W., Bayles, T. B., Massell, B. F., Forsham, P. H., Hill, S. R., Smith, S., and Warren, J. E.: Studies on the relation of pituitary-adrenal function to rheumatic disease, New England J. Med., 241:529-537, Oct. 6, 1949.

46. Wolfson, W. Q.: Role of the hormones in the pathogenesis and treatment of gout, Progress in Clinical Endocrinology, edited by S. Soskin, New York, Grune & Stratton. In press.

Anuria and Oliguria

A Review of Symptoms, Pathologic Physiology and Mortality Rates

PART I

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THIS presentation is concerned with (1) a summary of the pathogenesis and pathological physiology of anuria and (2) an inquiry into the reported incidence of medical anuria and oliguria and an analysis of the shortcomings in reporting these statistics. A following article (Part II) will be concerned with a rational approach to the treatment of anuria and oliguria and will contain a case history which illustrates the conservative mode of treatment used at the University of California Hospital during the past few years.

TYPES OF ANURIA*

Anurias have been classified as:

1. Pre-renal or circulatory, indicating that the causative lesion interferes with the supply of blood to the kidney;
2. Renal or excretory, implying an intrinsic lesion of the kidney;
3. Post-renal or eliminatory, reflecting obstruction of the urinary tract.

Obviously anuria is only a sign, since it may signify any one of these several situations.

The authors have been concerned mainly with the pre-renal and renal anurias which they have chosen to call medical anurias. Prolonged insufficient blood supply (pre-renal) to the kidneys ultimately leads to a lesion involving the lower nephron,[137, 138] so that it can be said that pre-renal disturbances lead to renal anuria. The authors have been particularly interested in this state, which is commonly known as lower nephron nephrosis. Post-renal anuria is often amenable to surgical or instrumental treatment. Since this subject is thoroughly covered in the urological literature, it will not be discussed here.

SYMPTOMS AND SIGNS

The symptoms and signs of uremia are generally well known. However, attention will be called to a few seen particularly in acute anuria.

Hypertension may or may not develop; its presence has been most variable in the cases observed or reviewed by the authors (nine instances in 28 patients). Question arose as to whether blood pressure is especially liable to rise with overhydration. Hoffman and Marshall[53] reported elevated blood pressure in all of their patients made edematous. In the authors' experience, the blood pressure returned to normal in most instances following recovery, if it had been previously normal.

Jaundice. It is noteworthy that in 28 cases of oliguria or anuria in our files, jaundice was observed in 13 patients, of whom four had undergone prostatectomy and eight had received whole blood transfusions immediately preceding the onset of anuria.

Hemorrhagic tendency. Anuric patients, like other patients with uremia, frequently have a hemorrhagic tendency manifested by petechiae, ecchymoses and gastrointestinal bleeding. Prothrombin concentration, bleeding and clotting time, and plasma vitamin C are not usually abnormal. The explanation of this tendency is not clear, and at present any therapy directed against it must be purely empirical.

Pain. Generalized muscle tenderness and severe muscle pain are occasionally found a few days after the onset of anuria. Patients also may develop muscular hyperirritability and hyper-reflexia. One of the authors (J. H.) has observed five patients in whom the mere touching of the muscles of the extremities elicited pain responses. Some patients experienced pain whenever they moved, and even the weight of the bed-clothes caused distress. Occasionally this "anuric type" of pain, with the muscle guarding which it involves, masquerades as "acute abdominal catastrophe" which may be a source of confusion to the surgeon. These phenomena lack adequate explanation. They are probably not due to vitamin deficiency, since they occur in well-nourished individuals and in the presence of massive vitamin therapy. They perhaps relate to accumulation of acid end-products.

Convulsions will be discussed under treatment in Part II.

PATHOLOGIC-PHYSIOLOGICAL CHANGES IN ANURIA

The physiological changes induced by anuria are similar to those occurring in complete nephrectomy. There is loss of the ability to eliminate non-protein nitrogen wastes and loss of control over electrolyte and water balance (osmotic pressure relationships). The adjustment of acid-base balance, normally shared by kidneys and lungs, must be accomplished solely through the pulmonary control of carbon dioxide.

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* Anuria literally means "no urine formation." Lattimer,[67] however, has arbitrarily defined anuria as a state in which the kidneys form 100 cc. or less of urine daily. The authors have used the term loosely and somewhat interchangeably with the word oliguria. In view of the probability that the underlying lesion is identical in both, this usage seems justifiable.

These changes are complicated by secondary effects: With the accumulation of acid metabolites, nausea and vomiting often occur, inducing electrolyte loss and also resulting in starvation. It will be recalled that, in starvation, glycogen stores are rapidly depleted and metabolic or energy needs must then be met by the catabolism of fat and protein. Protein catabolism, while furnishing glucose for essential needs (to the nervous system), releases nitrogenous end-products (mainly urea), potassium, and acids, such as sulfates and phosphates, which may reach toxic concentrations in the blood when not regulated by the kidneys. Fat catabolism, while supplying needed calories, leads to the formation of acetoacetic and betahydroxybutyric acids, thereby throwing an additional burden on the remaining mechanism for the adjustment of acid-base relationships.

Electrolytes. Since maintenance of electrolyte balance of the body fluids is largely under renal control, it is important to understand the alterations which loss of this control imposes.

It is convenient to divide electrolytes into two groups: (1) those serving osmotic pressure functions and (2) those with special physiological functions. A glance at Figure 1 will reveal that the main electrolytic cation of extracellular fluid is sodium. Because of its abundance in extracellular fluid, its small molecular weight* and its pharmacologic inertness,[42] sodium is able to serve as the most important cation in the maintenance of osmotic pressure. This role necessarily relates sodium closely to body water, so that, in the presence of normal renal function, sodium and water move together in the extracellular fluid and a constant relationship of sodium concentration to water is maintained.[28]

The other cations depicted in Figure 1 are present in little more than trace concentrations as compared to sodium. They are found in insufficient amounts to contribute more than a small share to osmotic pressure needs. On the other hand, through their pharmacodynamic action they exert a powerful influence on certain physiological functions. These functions have been frequently summarized and can be profitably reviewed.†

Since potassium accumulation in anuria can prove fatal,[112] only this pharmacodynamically active substance will be considered here. Potassium is abundant within cells, where it serves as the main intracellular base just as sodium serves extracellular fluid, and in a similar manner subserves osmotic pressure needs within cells. The potassium concentration of extracellular fluid is usually maintained at 3.8 to 5 meq. per liter of plasma. The normal kidneys excrete it rapidly when it is present in higher concentrations. Serum levels as high as 12 meq. per liter have been survived;[45] however, it

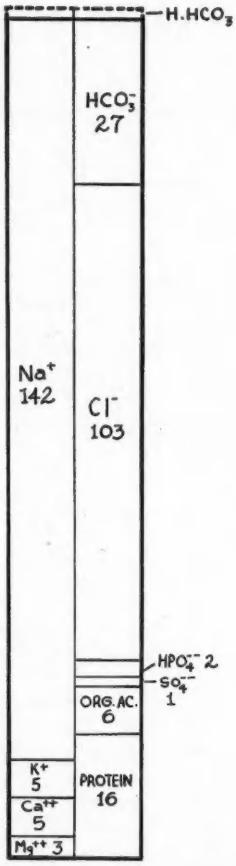

Figure 1 (adapted from Gamble).—The normal electrolyte composition of blood plasma (expressed as milliequivalents per liter of plasma).

seems improbable that this is frequent, as cardiac arrest in diastole is likely to occur even at lower concentrations.[127] Cellular catabolism accelerated by the starvation of vomiting produces an obligatory release of potassium into the extracellular fluids. Although this mechanism appears to be a realistic consideration in animals with anuria,[9, 32, 95, 143] it is apparently seen less often in man. The authors have observed only one patient in whom elevated serum potassium may have caused death. A possible explanation is that the treatment used has been focused on minimizing catabolic processes, thereby blocking potassium release from cells. Another explanation probably lies in the fact that the patients treated by the authors have not had crush syndrome. Strauss[128] recently mentioned an instance of potassium intoxication in lower nephron nephrosis.

In view of the potential toxicity of potassium accumulation, it is desirable to determine the serum potassium content in anuric patients at regular intervals. If this is not possible, serial electrocardiograms should be used for detecting changes related

* Osmotic pressure is directly proportional to the number of molecules per unit volume of fluid.

† See references 10, 15, 42, 55, 79, 84, 89, 106, 108, 123, 125, 142, 144, 145.

to potassium accumulation. These changes consist of (1) diminution in amplitude of the P wave, (2) widening and elevation of the T wave, and (3) S-T depression.[52, 144, 145] Serum potassium diminution is characterized by low amplitude or inversion of the T waves.

PATHOLOGY

There are several theories as to the basic physiological mechanisms which cause the anurias of transfusion reaction, crush syndrome, shock, burns, blackwater fever, and intravascular hemolysis.*

Most investigators[43, 78, 133, 135] now agree that the renal lesion is quite similar in anurias of the following states: Incompatible blood transfusion, intravascular hemolysis, crush syndrome, alkalosis, septic abortion, concealed accidental hemorrhage, cholera, yellow fever, sulfonamide toxicity; mercury, arsenic, bismuth and carbon tetrachloride poisoning; burns, shock, and blackwater fever. The typical picture is one of cortical ischemia and medullary vascular congestion. The tubular epithelium of the ascending loop of Henle and of the distal convoluted tubule shows degeneration and disintegration. The lumina are full of debris and the cells are flattened. The glomeruli remain nearly normal. The heavy metals tend to involve the proximal tubule more than the distal tubule.

Trueta and co-workers[135] in their recent work on renal blood flow reawakened interest in the mechanisms involved in renal shutdown. They were able to demonstrate in animals (rats and rabbits) a juxtamedullary vascular shunt which can cause the arterial blood supply to by-pass the cortex completely. This vascular shunt could be induced in one kidney by faradic stimulation of the proximal end of the cut sciatic nerve of the same side and by stimulation of the renal sympathetic plexus. Intravenous injection of pilocarpine nitrate, neostigmine, epinephrine hydrochloride, ephedrine hydrochloride, and the posterior pituitary hormones, Pituitrin® and Pitressin,® also produced the same shunting mechanism. In shock, this mechanism probably acts to protect the central nervous system from anoxia by insuring its blood flow despite a diminished circulatory volume; but prolonged operation of the shunt might cause renal ischemia and tubular degeneration. Van Slyke[138] found that complete renal anoxia of more than four hours' duration caused anuria in dogs.

The theory of tubular obstruction by abnormal pigments or detritus within the tubular lumen appears to be untenable since complete obstruction of *all* the tubules is never seen at autopsy, and since normal specific gravity and electrolyte content of the urine, expected if only some tubules were obstructed, is not seen in oliguria. On the basis of pathological lesions found in the tubules, Lucke[75] and Van Slyke[138] suggested that anuria is caused not by the failure of glomerular filtration but by the complete reabsorption of filtrate by damaged tubules.

* See references 3, 22, 23, 38, 43, 51, 67, 74, 75, 77, 78, 99, 101, 133-138.

REVIEW OF LITERATURE ON MORBIDITY AND MORTALITY OF ANURIA

In an effort to determine the fatality rate of nonobstructive or medical anurias, which is given variously as from 40 to 90 per cent, the authors have made a search of the literature from January 1943 to June 1947.

The most common causes of anuria were: (1) Intravascular hemolysis (20 cases with nine deaths—mortality, 45 per cent); (2) postoperative, postabortion, and postpartum renal damage (10 cases with two deaths—mortality, 20 per cent); (3) mercury poisoning (11 cases with eight deaths—mortality, 72.7 per cent); (4) shock (13 cases with nine deaths—mortality, 69.2 per cent); (5) sulfonamide toxicity or allergic reaction (16 cases with five deaths—mortality, 31.2 per cent).

The review* has been divided into two parts: (1) medical anuria, including cases attributable to sulfonamide toxicity when it was definitely stated by the authors that no sulfonamide crystals were seen in the urine or in the tubules at autopsy; (2) sulfonamide anuria due to crystalluria. Although inclined to believe that all sulfonamide anurias are the same, whether crystals are present or not, the authors have segregated anurias said to be due to sulfa toxicity from those said to be due to crystalluria because this has been done in the literature.

For several reasons, completely satisfactory conclusions could not be drawn from the statistics gathered. First, no one treatment has been accepted generally. As a result, patients with anuria are treated in such various and haphazard ways that recovery rates appear to depend more upon chance than upon the effect of therapy. Clearly, in such circumstances it is difficult to decide what the recovery rate should be. Secondly, in most hospitals there is a tendency to file under the diagnosis of anuria only the histories of patients who actually die with anuria; the histories of recovered patients are filed instead under the admission diagnosis or major diagnosis. For example, the University of California Hospital files show only 12 instances of anuria between January 1937 and June 1948, in a total of 80,956 hospital admissions; whereas one of the authors (J. H.) has in his private files the records of 17 patients with anuria observed in a period of only five years at the University of California Hospital. Armstrong, Freese and Hultgren[4] reported eight cases at Stanford University Hospital between 1935 and 1945, also a suspiciously low figure.

In Tables 1 and 2, "day of diuresis" and "day of death" are defined as the number of days after the onset of anuria that these events occurred. The day upon which the patient had urine output of 1,000 cc. or more, with increments thereafter, was designated the day of diuresis. Many papers reviewed did not mention specific days of diuresis or death; therefore, these figures were omitted in compiling the

* A few foreign journal references for these years which were not available in this country are not included in these statistics.

Cause of Anuria	No. of Cases	No. Recvrd.	Ave. Day Diuresis	Range	% Recvrd.	No. Died	Ave. Day Death	Range	% Died
Intravascular Hemolysis	20	11	10.1 [7]	4-12	55	9	11.3 [7]	6-17	45
Post Partum, Post Operative, Post Abortion	10	8	12.5 [6]	7-16	80	2	7 [2]	2-12	20
Black water Fever	1	1	11 [1]	—	100	0	—	—	—
Mercury Poisoning	11	3	9 [2]	8-10	27.3	8	18.8 [6]	4-24	72.7
Bismuth Toxicity	3	1	?	—	33.3	2	7.5 [2]	5-10	66.7
Crush Syndrome	5	3	3 [1]	—	60	2	9.5 [2]	7-12	40
Shock	13	4	2.3 [4]	2-3	30.8	9	7.8 [9]	3-17	69.2
Burns with Toxic Nephritis	2	0	0	—	0	2	5 [2]	2-8	100
Arsenical Poisoning	2	2	11.5 [2]	7-16	100	0	—	—	—
Carbon Tetrachloride Poisoning	2	1	10 [1]	—	50	1	10 [1]	10	50
Reflex Anuria	8	7	3.2 [8]	1-8	87.5	1	15 [1]	15	12.5
Hepato-Renal Syndrome	2	0	0	—	0	2	6 [2]	4-8	100
Diagnosis Miscellaneous	6	6	7.5 [6]	3-12	100	0	—	—	—
Sulfonamide Allergy or Toxicity	16	11	5.4 [7]	2-14	68.8	5	10 [5]	3-21	31.2
Total	101	58	7.3 [45]	2-16	57.4	43	10.4 [39]	2-24	42.6
Sulfonamide Crystal Anuria	84	82	3.1 [35]	1-11	97.6	2	3.5 [2]	3-4	2.4

Table 1.—Mortality according to cause of anuria. The 101 cases in the literature are segregated by causes of anuria. "Sulfonamide crystal anuria" is inserted below for comparison. The figures in brackets represent the number of cases from which each average is obtained. See text for full explanation.

Treatment	No. of Cases	No. Recvrd.	Ave. Day Diuresis	Range	% Recvrd.	No. Died	Ave. Day Death	Range	% Died
Renal Decapsulation	15	11	11.9 [6]	10-16	73.3	4	13.2 [4]	4-24	26.7
Forced Fluids	49	18	5.1 [15]	1-12	36.7	31	10 [31]	3-21	63.3
Fluid Restriction, Electrolyte Adjustment	17	14	9.9 [12]	3-14	83.3	3	7 [1]	7	16.7
Intravenous Procaine	3	3	6 [3]	3-9	100	0	0	0	0
Spinal Anesthesia	1	1	11 [1]	11	100	0	0	0	0
Splanchnic Block	4	2	6 [2]	6	50	2	11 [2]	10-12	50
Adrenal Cortical Ext.	3	2	2 [2]	2	67	1	4 [1]	4	33
Transfusions and Fluids to Combat Shock	12	1	2 [1]	2	8.3	11	7.5 [11]	3-15	91.7
Sodium Sulfate	5	3	3 [1]	3	60	2	13.5 [2]	6-21	40
Peritoneal Lavage	10	5	11.7 [3]	10-14	50	5	14.7 [3]	8-26	50
Ureteral Catheterization	3	2	2 [2]	2	67	1	7 [1]	7	33
Miscellaneous	7	4	8.3 [4]	1-16	57.1	3	17 [3]	7-26	42.9

Table 2.—Mortality according to type of treatment used in 101 cases reviewed from recent literature. Figures in brackets represent number of cases from which averages were computed. (See text) Total number of cases exceeds 101 since several patients received more than one type of therapy and accordingly are duplicated under the "Number of Cases" column.

averages. The numbers in brackets in Tables 1 and 2 indicate the number of cases in which a specific day was given for these events. Example: Table 1, intravascular hemolysis: Patients recovered, 11; average day of diuresis, 10.1(7). The average was figured on the basis of only seven cases, because data on the remaining four cases were insufficient.

In the 101 cases of medical anuria reviewed (Table 1), 58 patients recovered and 43 died, a mortality of 42.6 per cent. The average day of diuresis was 7.3; the average day of death was 10.4.

The most commonly used therapy (Table 2) was that of forced fluids (orally, rectally, or parenterally). Of the 49 patients so treated 31 died, a mortality of 63.3 per cent. With another form of the same treatment, transfusions and fluids to combat shock, 11 of 12 patients died, a mortality of 91.7 per cent. In the latter instance, an average day of death of 7.5 indicates that the patients were not dying from the shock itself. The lowest mortality rate occurred in the group of patients whose fluid intake was restricted and in whom an attempt was made to maintain electrolyte balance (17 cases with 14 recoveries—mortality, 17.6 per cent).

Study of the treatment used on the 43 patients who subsequently died is instructive. Thirty were treated by forced fluids, alone or in combination with some other therapy; five by peritoneal dialysis; two by the use of artificial kidney; two by means of renal decapsulation (one by forced fluids and renal decapsulation together); one each by reciprocal blood transfusions, restriction of fluids, transfusion and fluids to combat shock; and one by treatment not specified. In many instances autopsies were not done. When they were done, few of the necropsy findings were included in the case reports. A striking fact is that overhydration, observed either clinically or at autopsy, was commonly found. The authors considered one or more of the following as evidence of overhydration: Peripheral edema, pulmonary edema, pleural or pericardial effusions, and ascites.

In 21 of the 43 cases in which death occurred, there was definite mention of excessive hydration at the time of death. In 14 cases, there was no mention of any particular clinical or necropsy findings at death. In eight of these 14 cases, fluids had been forced. By relating fluid intake in these patients to known values for extracellular fluid volume, it was obvious that overhydration was probable but was overlooked as unimportant and was not mentioned by the authors. There were three deaths due to bowel perforation and peritonitis from mercury poisoning; two in which renal damage alone was mentioned; three unavoidable deaths not due to uremia; and one each from intracranial hemorrhage, multiple pulmonary infarcts, and mercury gostroenteritis with nephritis and bronchopneumonia.

Lattimer[67] mentioned a patient anuric 37 days and oliguric 13 days who was kept alive by skillful management of electrolyte balance and fluid administration. He described another patient who died after 21 days in anuria. More recently, Strauss[128] mentioned similar instances.

Burwell, Kinney, and Finch,[17] in a recent review of the literature, found 34 cases of anuria due to intravascular hemolysis in which the day of diuresis ranged from 1 to 16. The authors' review (Table 1) and experience indicate an identical range. Lattimer[67] and Strauss[128] cited several cases in which patients recovered after longer periods of anuria; Strauss pointed out that in the days before intravenous fluid therapy it was not unusual for a patient to live 25 days or longer in complete anuria. The authors believe that in uncomplicated anuria death before the tenth to the sixteenth day implies inadequate treatment. Only six of the 43 deaths noted in a review of the literature occurred after the 16th day of anuria. In addition, there were five unavoidable deaths—one due to pulmonary infarction, one to cerebral hemorrhage, and three to bowel perforation from mercury gastroenteritis. As there were 11 unavoidable deaths in 101 cases reviewed, theoretically the mortality rate could have been 10.9 per cent. The actual mortality rate was 42.6 per cent.

It is of interest to note that in the anuria accompanied by sulfonamide crystalluria, the mortality is only 2.4 per cent in a series of 84 cases. The two patients who did not recover were treated by forcing fluids and died in pulmonary edema within four days after the onset of anuria, clearly toon soon for the ill effects of uremia. Although cystoscopy and ureteral catheterization with lavage are extensively used for individuals with sulfa anuria, spontaneous recovery occurred within four days in most patients who were treated conservatively, and in only one of the 84 cases was diuresis delayed until the eighth day.

The urological service at the University of California Hospital has adopted a conservative approach to the treatment of anuria and rarely performs cystoscopies or ureteral catheterizations because of sulfa crystalluria. There have been no deaths accompanying sulfa crystalluria in the University of California Hospital.

In summary, Tables 1 and 2 indicate a mortality from anuria of 42.6 per cent. In the authors' opinion the percentage is this high because it excludes the statistics on recovered patients. Further, an analysis of the statistics on the patients who died shows that, with the exception of deaths from mercury poisoning, the high mortality rates relate as much to the treatment as to the cause of the anuria. The lowest mortality, 13.6 per cent, was in the group of patients for whom fluid intake was restricted and in whom an attempt was made to maintain electrolyte balance. Mortality was highest in groups in which fluids were forced.

TYPES OF TREATMENT

The treatment with blood and blood substitutes of pre-renal failure due to shock is well known and will not be discussed here. Since shock tends to be progressive once it is established, it is unlikely that

it can act as more than a temporary or initiating factor in anuria. As mentioned previously, recent developments in the therapy of maintained anuria or oliguria have been formulated in the belief that such anuria or oliguria is caused by a lesion of the lower nephron. Accordingly, therapy has been aimed at maintaining life long enough to permit tubular regeneration. Various treatments have been designed to gain this time. Repair processes begin promptly after the removal of the responsible agent and are usually complete enough by the eighth to 14th day for the kidneys to resume partial function, thereby bringing about urine output. Clearly, renal decapsulation, intravenous administration of procaine, spinal anesthesia, splanchnic block, caudal block and the like are treatments predating the concept of the lower nephron lesion as a cause of anuria.

Renal decapsulation. There are two current theories as to how renal decapsulation works: (1) it releases intrarenal pressure, thus allowing nephrons to function again; (2) it destroys the sympathetic control of the renal vascular system and permits vasodilatation which leads to resumption of the normal function of the nephrons. Hinman,[52] reviewing 156 patients with mercury poison anuria who were treated by decapsulation, reported recovery in 14; Brenner[14] reported 59 patients given similar treatment, with 14 recoveries. This amounts to a total of 215 cases with 28 recoveries or a mortality of 87 per cent, which is slightly higher than the 72.7 per cent mortality in the 11 patients with mercury poisoning who were treated in the various ways shown in Table 1.

Peters[111-113] recommended decapsulation to relieve increased intrarenal pressure within the first 24 hours in the case of anuria due to crush injury and transfusion reaction. He omitted data, however, concerning the subsequent onset of diuresis, which is essential for judging the efficacy of decapsulation. If the intrarenal pressure theory is correct, diuresis would be expected to occur immediately after operation.

Table 2 lists 15 cases of acute medical anuria (all types) in which the patients were treated by unilateral or bilateral renal decapsulation. The average day of diuresis was 11.9. The average day of operation was after 5.4 days of anuria, with a range of three to 11 days. There was not a single case in which diuresis occurred before the third postoperative day. In all instances the course of the anuria bore no immediate relationship to the decapsulation, and the onset of diuresis fits into the sequence of events seen in the natural course of anuria in which decapsulation has not been done.[132]

Van Houtum and Covarrubias[136] have expressed the feeling that decapsulation has a definite place as a treatment for the relief of anuria caused by acute glomerulonephritis. They postulated that destruction of the renal sympathetic nerves induces diuresis. As examples, they cited two cases in which the relief of anuria of five and six days' duration occurred immediately after operation. A case reported by Hoffman and Marshall[53] vividly illustrates the difficulty of evaluating the effects of decapsulation.

Intravenous administration of procaine. Procaine given intravenously as a treatment for anuria has been recommended by European workers. Theoretically, it anesthetizes the renal sympathetic nerves, which permits vasodilatation. Masselot[85] reported that one patient given procaine intravenously on the seventh day of anuria voided 700 cc. of urine during the next 24 hours. Langeron, Paget, and Michaux[66] reported a case of sulfonamide anaphylaxis with anuria completely relieved 24 hours after the intravenous administration of three 100 mg. doses of procaine at two-hour intervals; diuresis occurred on the third day of anuria. Loeper and Sterboul[72] reported that a patient given 150 mg. of procaine intravenously on the second day of anuria did not have diuresis until the seventh day. Although it is possible that intravenous administration of procaine may be of some benefit, there is insufficient evidence to suggest that the anuria would not have been relieved without it.

Spinal anesthesia,[81, 116] *splanchnic block,** and *caudal block anesthesia*[128] have all been used with the idea of producing renal vasodilation, despite the fact that anuria is sometimes a sequel to such procedures.

Vividialysis in its several forms—(1) peritoneal dialysis, (2) small and large bowel perfusion, gastric lavage, and (3) dialysis of the patient's blood with a mechanical kidney—has been employed extensively with varying success in attempts to remove metabolic waste products from patients in renal failure.

1. *Peritoneal dialysis* has been used by Pearson,[103] Frank, Seligman and Fine,[39] Abbott and Shea,[1] and many others[92] within the past four years. The notable defect of this technique is the frequency of infection despite the use of antibiotics. Although nitrogenous end-products can be removed by this technique, its many difficulties outweigh its practicability.

2. *Small and large bowel perfusion* has been used in both animals and man by many investigators.[96, 100, 104, 117, 141] Continuous lavage of the colon has been employed by Daugherty, Odell, and Ferris.[29] Numerous demonstrations have shown that nitrogenous end-products can be removed effectively if a sufficient length of small bowel is perfused with sufficient fluid. This technique, like that of transperitoneal perfusion, is beset with difficulties. Notable among these is that of controlling water accumulation and that of preventing the development of paralytic ileus. The large bowel has proved a relatively ineffective route for removing nitrogenous end-products. Its use as a dialysing membrane is complicated by its particular ability to absorb fluid and electrolytes. The available surface in the stomach is inadequate and the exchange is limited.

* See references 20, 47, 72, 114, 122.

3. *Mechanical kidneys*[2, 60, 61, 94] which make use of dialysis ordinarily require a long semipermeable cellophane tubing, through which the subject's blood is passed. Dialysis of unwanted materials is made across the membrane into a surrounding heated fluid bath. This technique requires the use of anticoagulants and of the necessary blood assays to prevent hemorrhage. Usually the artificial kidney requires so much blood that it must be primed with compatible donor blood. Care and control of the equipment are complicated and demand competent technical help and elaborate laboratory facilities. As yet, the results obtained with mechanical kidneys have not shown this method to be superior to more conservative measures.

Reciprocal blood transfusions,[121, 124] although little used, are of great interest and undoubtedly have been insufficiently explored in the treatment of anuria.

Resin exchange mechanisms[8, 64, 91] are of interest in that exchange resins may be administered enterally. Since it is not known what components of the blood should be removed in order to maintain life in the absence of renal function, methods more closely imitating renal mechanisms (viz., dialysis) may be more desirable. Resin exchange kidneys, however, merit careful and extended study.

Testosterone[49, 86] through its protein anabolic action is said to exert a favorable influence in the presence of renal failure. The efficacy of this measure in relieving the toxemia of uremia or in prolonging life has not been convincingly demonstrated. In any circumstances it cannot be considered as more than an adjunct to other measures.

Water overloading. Although frequently done inadvertently, water overloading has not been advocated until recently as a mode of treatment in anuria. Hoffman and Marshall,[53] while recognizing its danger, suggested that in patients with competent circulatory systems, the end-products of catabolism can be rendered less toxic by dilution in induced edematous fluid. The treatment, which will be discussed in Part II of this article, is based upon the assumption that the danger of heart failure and pulmonary edema outweighs the beneficial effects of dilution, and that accumulation of toxic products can be delayed sufficiently by other means.

Diuretics will be discussed in Part II.

This is Part I of an article in two parts. Part II, with a list of references for both parts, will appear in a succeeding issue.

The Use of the Male California Toad in the Diagnosis of Pregnancy

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SUMMARY

The California male toad, readily available in most areas of the state, and for many other reasons a better subject for test purposes than the frog, was used in 237 tests to determine the presence or absence of pregnancy in humans. Human urine was injected into the toads, and the cloacal discharge then was examined for the presence of sperm. There were only two false reactions in the series—both false negative. In subsequent tests in both these cases, the result was positive.

AMONG the forerunners of present-day frog tests for pregnancy was the technique described by Shapiro and Zwarenstein in which they utilized the female South African clawed frog (Xenopus laevis). Bellerby,[1] in 1934, also reported favorably on the accuracy and simplicity of this test.

Galli-Mainini,[2] in 1947, demonstrated that the male South American toad (Bufo arenarum Hensel) emitted spermatozoa after stimulation with mammalian chorionic gonadotropin. Previously, Robbins and Parker[3] had demonstrated this reaction in the male frog.

That the common North American male frog (Rana pipiens) is an excellent and easily available test animal for the diagnosis of pregnancy has been pointedly emphasized in the work of Wiltberger and Miller[4] (1948) and Robbins and Parker[3] (1948).

The basic physiology of the Aschheim-Zondek, Friedman, rat hyperemia and frog tests consists of animal assay methods of detecting increased levels of pregnancy hormones.

In the opinion of numerous competent workers, frog tests are not only simpler, more rapid, and more economical but are apparently more sensitive in the diagnosis of early pregnancy.

In positive reactions the female frog responds by the extrusion of grossly visible ova; the male frog by the ejaculation of spermatozoa which are readily distinguishable by the microscopic examination of fluid from the external cloacal orifice.

The accuracy and speed of the male Rana pipiens test has been duplicated by the author of this article in a technique utilizing the male California toad (Bufo boreas halophilus).

The reason for the choice of this toad was its wide distribution throughout California except in deserts and highest mountains. Easier to obtain and handle, the toad presents no problems in feeding, maintenance and (important) differentiation of sex. It is the male that does the vocalizing: A sweet falsetto trill, birdlike in character, reminding the listener of the prairie chicken, or quail. Handle the male toad, stroke it or shake it, and it will usually set up an audible protest. The female California toad is inarticulate, somewhat larger and more heavily built. During the regular breeding season (January to May) the skin of the female remains rough, whereas that of the male becomes smooth. The males usually have areas of rough, dark-colored skin on the "thumb" and inner sides of two adjacent "fingers."

Toads readily adjust themselves to artificial living conditions. For practical purposes all that is required is a box containing gravel and garden soil (light and loose for burrowing purposes) with a tray or pan filled with water at one end. The top of the box is covered with chicken wire and an electric light bulb is suspended over it in order to attract flying insects at night. This arrangement may be modified by laying the box on its side, thereby providing a wooden "ceiling" which may be hinged to facilitate handling.

Being cold-blooded vertebrates, toads, like frogs, may be induced into a state of artificial hibernation by storage in the laboratory refrigerator at temperatures not lower than 4° C. Under these conditions metabolic activity is so little that the various vital functions are carried on at the lowest possible levels and the animals are kept "fresh" for long periods. Undoubtedly, also, the ample reserve food supply of the toad (stored in fat, muscle, liver and elsewhere) is used up partly for fuel to keep the spark of life smouldering and partly for elaborating the sexual products.

The California toad, and toads in general (of the genus Bufo), may be distinguished from other tailless amphibians by the presence of a large raised area, the parotid gland, on each "shoulder" behind the ear membrane. The age of the adult California toad is two to three years. Other physical characteristics are: Dry skin with numerous large "warts"; upper surface grayish-green, with many large, irregular spots or streaks of black; a conspicuous streak of white extending along and down the middle of head and back; undersurface dull yellow, sometimes with numerous small black spots; hind legs only twice as long as forelegs; jaws without teeth; head-and-body length (snout to vent) ranging from 3½ to 4½ inches.

Bufo boreas halophilus is such a heavy-bodied

animal that it seldom hops in the conventional manner. When not frightened it walks in slow fashion, dragging the hind feet so that the toes are continually in contact with the ground. It breeds in ponds and quiet water of streams, irrigation ditches and "reservoirs" on farming land. Its non-breeding habitat is on or a little below the surface of the ground, wherever shelter can be found—often in gardens, parks and golf courses. It feeds on all kinds of insects and worms. It is easier to capture that the slippery, agile frog. Sufficient numbers may be obtained by advertising in local newspapers. Other good sources of supply are frog farms in the larger cities and biology classes at local schools.

Toads are carnivorous. Their favorite food consists of insects, worms, small fishes and the young of their own or allied species. Earthworms seem to be especially relished. Canned turtle food, fish food and even morsels of meat such as hamburger may be dropped directly into their buccal cavity by prying open their jaws. Toads usually retain and swallow much food whereas the frog is more liable to regurgitate it. Twice-weekly forcible feedings undoubtedly are of some value in restoring vitality to recently used animals.

Upon dissection, both male and female reproductive systems of the toad are found to be rather intimately associated with the excretory system. The male system consists of a pair of yellow oval testes, lying against the dorsal wall in contact with the kidneys. The testes have no ducts of their own, but send forth their products through the ducts of the kidneys. Attached to the anterior part of the testis is a fat-body, composed of orange-colored finger-like masses. These become very large in the summer and act as reserves of food in later months.

The female reproductive system consists of two large egg masses or ovaries. Beside each ovary is its long, large white coiled oviduct.

Toads may be killed for dissection by subcutaneous injection of chloral hydrate solution (a few crystals dissolved in 3 cc. of water) or by plunging a sharp instrument into the brain at the base of the skull.

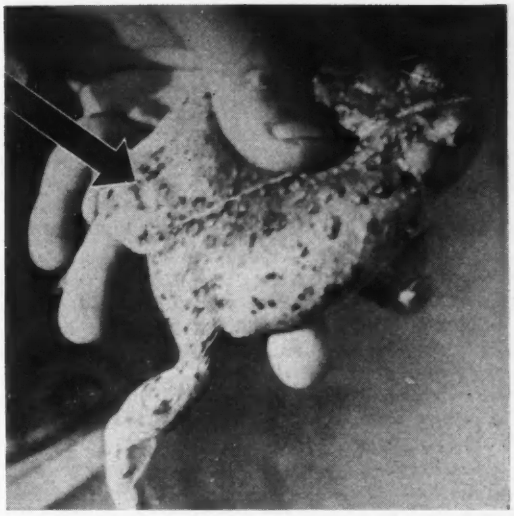
By the use of the male California toad, as with the Rana pipiens, laboratory diagnosis of pregnancy can be carried out within two to three hours, often sooner. The endpoint is unequivocal; sperm is either present or absent.

TECHNIQUE

The following technique is based on analyses on 237 specimens of urine from the sources shown in Table 1. Accuracy of 99 per cent was attained.

Technique.

Collect the first morning specimen of urine, which is a concentrated one, in a clean container, not necessarily sterile. Random specimens with a not too dilute specific gravity have proven satisfactory. Centrifuge, filter or let stand to clarify. Without adjustment of pH or control of temperature, inject



The male California toad (Bufo boreas halophilus). Recommended method of injecting urine into subcutaneous dorsal lymph sac. Needle (arrow) is directed toward median line just above the upper cloacal fold.

5 to 10 cc. subcutaneously into the dorsal lymph sac of each of a pair of male toads. Thrust the needle (22 gauge) superficially into the upper thigh muscle area, directing the point to the midline just above the upper cloacal fold near the acetabulum.

Beginning one hour later obtain fluid, using a glass pipette, from the external cloacal orifice and examine under the low power lens of the microscope with reduced light. Spermatozoa, usually actively motile, are very readily seen if present. This is a positive reaction. The long, undulating flagellum of the individual sperm is easily distinguishable when the high power lens is used.

A negative reaction is reported when no sperm is seen during a three-hour period of observation following inoculation with the test urine. In certain cases in which the reaction is negative, urine from a woman known to be pregnant is administered in order to demonstrate the ability of the toads used to respond to the presence of the chorionic hormone.

Occasionally the urine proves to be toxic, either killing the toad or rendering it very ill. If another specimen cannot be conveniently obtained, the split-dosage technique of Robbins and Parker may be employed: Two half-doses given an hour apart.

TABLE 1.—*Results of Toad Tests for Frequency*

Source of urine	Correct Positive	Correct Negative	False Positive	False Negative
Pregnant women	136	....	....	2
Women with amenorrhea without pregnancy	....	63	0	....
Normal women with menses	....	36	0	....
	136	99	0	2

Before giving the second injection it is advisable to make an examination of cloacal fluid, as a positive reaction may already be discernible at this stage.

NOTES

After a resting and feeding period of at least three weeks in a separate terrarium, animals which have been shown to react positively may be reused.

The toxicity of certain urines is most often due to drugs (ergot, quinine, morphine, codeine, sulfa drugs and even acetylsalicylic acid). The patient should abstain from taking drugs prior to collection of the specimen.

Blood serum and urine may be used interchangeably. It is claimed that, in the interests of a less toxic, more constant source of hormone, blood serum appears to be preferable. However, many laboratory technicians favor the use of urine over serum.

If a negative report is obtained on a specimen voided less than seven days after the first missed menstrual period, the test should be repeated later.

As the initial step in the Bufo test the author deems it wise to examine a cloacal smear prior to inoculation to rule out the spontaneous presence of sperm.

CONCENTRATION METHOD

A rapid concentration method may be used upon encountering certain urines suspected to contain a low hormone titer: Adjust entire collection of urine to a pH less than 4.5 by adding hydrochloric acid drop by drop until nitrazene paper turns sharply lemon yellow and blue litmus turns sharply red. Place all of specimen in a 1000-cc. graduated cylinder and mix with 2 volumes of acetone. Let stand or centrifuge to collect sediment. Pool sediment in centrifuge tube and wash with ether, mashing and spreading sediment along sides of tube with an applicator stick. Decant ether (or centrifuge) and run current of air over sediment until dry. Dissolve sediment with 3 to 4 cc. of water, using same applicator stick (which has remained in tube) to disperse and break up clumps. Centrifuge and adjust supernatant to pH 5.5 or pH 6.00 with sulfosalicylic acid. Inject half-portions of this into each of a pair of male toads.

DISCUSSION

Duplicate tests utilizing Rana pipiens were conducted in every instance in this series of 237 tests with the California toad. Occasionally rabbits were employed to corroborate certain negative findings. No discrepancies were noted.

In this series two false negative reactions were obtained. Tests with urine specimens collected one week later, in both cases, gave positive results. In connection with the false negative reactions, various possibilities may be mentioned: (1) Low hormone titer (specimens collected too early?); (2) use of immature toads (only those definitely measuring over 3½ inches from snout to vent should be selected); (3) presence of inhibitors or depressants due to drugs, medicines, etc.; (4) urine of very low specific gravity. The following guide for determining the dose from the specific gravity is recommended:

Specific Gravity	Dose
Under 1.012	10 cc.
1.013 to 1.019	8 cc.
1.020 to 1.029	6 cc.
1.030 and over	5 cc.

P. O. Box 1201.

REFERENCES

1. Bellerby, C. W.: Rapid test for diagnosis of pregnancy, Nature, London, 133:494, March 31, 1934.

2. Galli-Mainini, C.: Pregnancy test using the male toad, J. Clin. Endocrinology, 7:653, Sept. 1947.

3. Robbins, S. L., and Parker, F., Jr.: Use of male North American frog (Rana pipiens) in diagnosis of pregnancy, Endocrinology, 42:237-243, April 1948.

4. Wiltberger, P. B., and Miller, D. F. P.: Male frog, Rana pipiens, as new test animal for early pregnancy, Science, 107:198, Feb. 20, 1948.

Chloramphenicol in the Treatment of Typhoid Fever

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SUMMARY

Six patients with typhoid fever were treated with chloramphenicol. The excellent clinical response in four cases suggests that chloramphenicol is the drug of choice in the treatment of this disease. In one case in which clinical relapse occurred, there was good response to re-treatment. One patient, critically ill, in a typhoid state, and treated late in the course of the disease, died without beneficial effect from chloramphenicol, but the patient had been unable to retain the drug because of vomiting.

THE new antibiotic chloramphenicol has been demonstrated to be effective in the treatment of typhoid fever. E. typhosa has been shown to be sensitive in vitro to less than one microgram per milliliter of chloramphenicol.[2, 6] It is well absorbed from the gastrointestinal tract, is only given orally and is effective by that route. Toxicity has proven to be low both experimentally in animals and in the treatment of human infections.[3, 6] Treatment of typhoid fever with chloramphenicol was first favorably reported by Woodward and his collaborators[8] from the Institute for Medical Research, Kuala Lumpur, Malaya. Ten patients were treated with prompt response in all, blood cultures becoming negative and fever subsiding in the average time of three and one-half days. There were two instances of relapse after afebrile periods of ten and 16 days, but in both cases the patients responded to a second course of therapy and no increased resistance to the antibiotic was shown. The total dosage of chloramphenicol per patient averaged 19.1 gm. given over periods averaging 8.1 days. The dosage schedule was 50 mg. per kilogram of body weight as an initial dose, followed by 0.25 gm. every two hours until the temperature was normal, and then every three to four hours for five days. Woodward[9] more recently reported on 21 additional patients with typhoid fever treated with chloramphenicol with uniformly favorable results. There were four relapses, two instances of intestinal hemorrhage, and one case of perforation complicated by peritonitis. One patient died during convalescence with a massive pulmonary embolus. Recent reports by McDermott and co-workers[4] and Stiller[7] on the use of chloramphenicol in typhoid fever indicate that it is efficacious in the treatment of this disease. At present, due to the previous scarcity of this antibiotic, few published reports on the treatment of typhoid fever with chloramphenicol are available. The following is a report of six cases of typhoid fever treated with chloramphenicol.

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CASE REPORTS

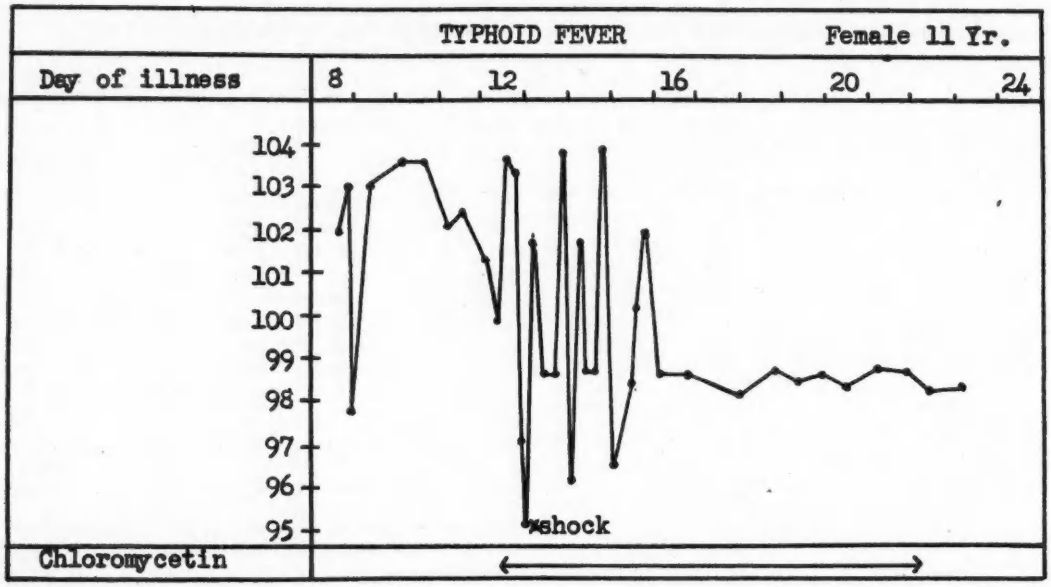
CASE 1: An 11-year-old Mexican girl, living in Los Angeles County, was admitted to the contagious disease unit of the Los Angeles County General Hospital on March 20, 1949. The illness began March 12 with dry cough, fever and shaking chills. Fever was elevated to 104° F. in the late afternoon and shaking chills recurred the night before admission to the hospital. Diarrhea accompanied by vomiting occurred during the first week of illness and lasted three days. The patient complained of slight sore throat and vague generalized abdominal pain for several days before hospitalization. There was no history of rash or bloody stools. A physician had treated the patient with four injections of penicillin and oral sulfonamides. Two brothers had had typhoid fever three years before and were in contact with the patient.

The patient was acutely ill, but oriented and rational. The temperature was 102° F., the pulse rate 96, respirations 18 per minute, the blood pressure 150 mm. of mercury systolic and 70 mm. diastolic, and the body weight 99 pounds. There was no rash. The right tympanic membrane was mildly injected and there was slight injection of the pharynx. There was a soft basal systolic murmur, grade 1. The lungs were clear. There was active intestinal peristalsis. The spleen was not palpable.

The urine was normal. Hemoglobin content of the blood was 14.5 gm. per 100 cc. Leukocytes numbered 9,400 with 70 per cent neutrophils. Subsequent counts remained constant. The CO_2 combining power was 38 volumes per cent and the non-protein nitrogen was 29 mg. per 100 cc. of blood. The prothrombin was 34 per cent of normal. X-ray films of the chest showed no abnormality. Agglutination for E. typhosa was positive in dilution of 1:320 and negative for Para A, Para B, OX-19, and Brucella. Blood cultures were positive for E. typhosa on March 20 and 23, but showed no growth on March 27 and 30. Cultures of urine taken by catheter on April 8, 14 and 19, showed no growth for E. typhosa, but the first culture contained staphylococcus albus. Three stool cultures taken on April 9, 14 and 19 showed no growth for E. typhosa.

The patient's course during the first four days of hospitalization was that of an acute infection. She became lethargic with fever to 103.6° F. A few small rose spots were noted on the abdomen and extremities. The patient was treated symptomatically until March 24, the fourth hospital day, when chloramphenicol was started. An initial dose of 2.5 gm. suspended in water was given orally, followed by 0.25 gm. every two hours until March 29, when the dose was reduced to 0.25 gm. every four hours and continued to April 2. A total of 18 gm. was given during this ten-day

CHART 1.—*Range of Temperature (Case 1) from Day of Hospitalization*



period. Administration of chloramphenicol was started on the 12th day of illness and the patient became afebrile 67 hours later. Seven and one-half hours after the first dose of the antibiotic the patient went into shock, became cold and clammy, with profuse perspiration, drop in blood pressure to 80 mm. of mercury systolic and 20 mm. diastolic, and a precipitous drop in temperature from 103.6° F. to 95.2° F. (Chart 1). She responded well to routine shock therapy. Each evening on the two following days similar precipitous drops in temperature, to 96° F. and 96.4° F., respectively, took place without further manifestation of shock. Subjective improvement began within 24 hours after the chloramphenicol had been started. The patient recovered uneventfully and was discharged cured on April 28.

CASE 2: A 14-month-old white female infant was admitted with typhoid fever from the Children's Hospital to the contagious disease unit of the Los Angeles County General Hospital March 25, 1949. She had entered the Children's Hospital March 22 with a history of rhinitis, slight non-productive cough, and fever of 12 days' duration. Fever was remittent up to 101° F. rectally during the first five days, gradually rising to 104° F. The patient had been examined by the family physician four days before hospitalization and had been given penicillin. A red rash promptly developed over the nose and cheeks; it subsided in two days and was followed by desquamation. Immediately thereafter a widely scattered red papular rash appeared on the trunk and it persisted up to the time of hospitalization. On the day before admission a sulfonamide was given orally and one injection of penicillin was administered. There was a history of contact with the owner of the patient's apartment who had had typhoid fever about 30 years previously.

Upon physical examination at the Children's Hospital, the child was noted to be acutely ill with large scaling nonerythematous areas over the nose, cheeks, and above the left eye. There were widely scattered pinhead erythematous maculopapular rose spots over the trunk which faded with pressure. Rectal temperature was 104.5° F. The left tympanic membrane was dull. The throat was mildly injected and boggy. The heart and lungs were normal. The abdomen was soft. The liver and spleen were not palpable.

Urinalysis showed one plus albumin. The hemoglobin was 8.5 gm. per 100 cc., and leukocytes numbered 12,000 with 72 per cent neutrophils, 26 per cent lymphocytes, and 1 per cent each of monocytes and plasma cells. Roentgen-ray examination of the chest showed no abnormality. The spinal fluid was clear; it contained one cell per cu. mm.; reaction to Pandy's test was negative and there was no growth on a culture. Agglutination for typhoid antigen was positive in a dilution of 1:320 and negative for Para A, Para B, and Brucella. Blood and urine cultures were positive for E. typhosa.

The patient was given 30,000 units of penicillin every four hours until transfer to the Los Angeles County General Hospital. Fever continued at 104° F. for two days and then fluctuated between 100° F. and 104° F. rectally. Shortly after admission the spleen became palpable.

On admission to the contagious disease unit of the Los Angeles County General Hospital the patient was acutely ill, pale, toxic, and irritable when disturbed. The rectal temperature was 103° F., the pulse rate 130, respirations 26 per minute and the weight 28 pounds. There were numerous rose spots on the trunk which faded with pressure. Slight residual desquamation of the face persisted. The pharynx was slightly injected. The heart and lungs were normal. The abdomen was slightly distended and the tip of the spleen palpable.

Results of urinalysis were normal. Hemoglobin content of the blood was 9 gm. per 100 cc.; erythrocytes numbered 4,030,000, and leukocytes 9,700 with 55 per cent neutrophils. Following three successive daily blood transfusions, the hemoglobin was 15 gm., erythrocytes numbered 5,090,000 and leukocytes 9,700 with 51 per cent neutrophils. The blood CO_2 combining power was 45 volumes per cent and the non-protein nitrogen content was 20 mg. per 100 ml. of blood. Agglutination for E. typhosa was positive in dilution of 1:320 and negative for Para A, Para B, OX-19, and Brucella. There was no growth on a blood culture on March 28. Catheterized urine cultures were negative for E.

typhosa and positive for non-hemolytic (gamma) streptococcus on March 25, positive for E. coli, aerobacter aerogenes and proteus vulgaris on April 7, and negative on April 14 and 19. Four stool examinations were negative for E. typhosa.

The patient's course was acute during the first four days with remittent fever to 105° rectally. There were frequent loose green stools during the first few days. The patient was irritable, dehydrated, had slight abdominal distention, and refused oral feedings. Intravenous fluids and glucose and 150 ml. blood transfusions were given on three successive days. Fluids and food were also given by Levine tube. The patient was hydrated but continued toxic and acutely ill. Chloramphenicol was started March 28, approximately 18 days after the onset of illness with an initial oral dose of 0.75 gm. suspended in water, followed by 0.25 gm. every two hours until March 31, when the dose was reduced to 0.25 gm. every four hours until April 5. A total of 10 gm. was given during eight days. The patient became afebrile approximately 76 hours after therapy was started. Gradual improvement was noted during the first few days of treatment, the fever subsiding, and the patient appearing clinically well several days prior to the discontinuance of treatment. Recovery was uneventful and the patient was discharged cured on April 28.

CASE 3: A 12-year-old white boy was admitted to the contagious disease unit of the Los Angeles County General Hospital on May 3, 1949, with typhoid fever. The present illness began abruptly on April 23 with high fever, daily bed-shaking chills, headache, vomiting and general malaise. The patient had been able to retain fluids the first few days, but vomited occasionally until entering the hospital. He had diarrhea but no bloody stools. Fever remained high with severe intermittent bed-shaking chills. He had been given 300,000 units of penicillin in procaine and oil several days after the onset of illness, by the family physician at home, with no effect on the clinical course. The patient was admitted to the Huntington Memorial Hospital, Pasadena, where aureomycin was given for two days without effect. A culture of the blood on the second day at the Huntington Hospital was positive for E. typhosa. The patient was then transferred to the contagious disease unit for treatment. Grandmother and mother had had typhoid fever some years before and were in contact with the patient.

Upon physical examination, the patient was noted to be obese. He was not acutely ill and was in no immediate distress. He complained only of headache and shaking chills. The temperature was 101.2° F., the pulse rate 90, respirations 28 per minute, the blood pressure 120 mm. of mercury systolic and 80 diastolic. The body weight was 200 pounds. There was no rash. The left tympanic membrane was slightly injected. The heart and lungs were normal. There was slight tenderness in the left hypochondrium. Peristalsis was active. The spleen was not palpable but was enlarged to percussion.

Results of urinalysis were normal. Hemoglobin content of the blood was 15 gm. per 100 cc. Leukocytes numbered 7,400 with 76 per cent neutrophils, 15 per cent lymphocytes and 9 per cent monocytes. Subsequent counts remained fairly constant. The prothrombin was 80 per cent of normal. In a number of determinations, the icteric index ranged between 10 and 12 units. The CO_2 combining power was 60 volumes per cent and the non-protein nitrogen 25 mg. per 100 cc. of blood. The serum albumin was 4.4 gm. and the globulin 2.2 gm. per 100 cc. A blood culture was positive for E. typhosa on admission and subsequently during a relapse. Agglutination for E. typhosa was positive in dilution of 1:160 and negative for Para A, Para B, OX-19, and Brucella. Numerous cultures of catheterized urine and of stools were negative for E. typhosa.

Chloramphenicol was started several hours after admission to the hospital on May 3, with an initial oral dose of 2.25 gm. suspended in water, followed by 0.25 gm. every two hours until May 6, when the dose was reduced to 0.25 gm. every four hours. The patient became afebrile in 48 hours. On May 9, the dose was increased to 0.75 gm. every four hours because of a relapse with the temperature going to 101.8° F. The temperature returned to normal in 12 hours. This dose was continued to May 14 when the drug was stopped. Subjective improvement in the patient's condition was noted within 48 hours after chloramphenicol was started. He was vomiting on admission but was subsequently able to retain food and the drug. A dicrotic pulse was noted the second day after admission. The patient's complaints ceased until May 26 when a second relapse occurred, characterized by severe headache, marked restlessness, general malaise, and fever. On the day of the second relapse a blood culture taken was positive for E. typhosa and the agglutination at the same time was positive in dilution of 1:160. Chloramphenicol therapy was reinstituted and the response was prompt. The temperature again returned to normal in 72 hours. In this course of treatment an initial dose of 2.25 gm. was followed by 0.5 gm. every two hours until June 6, when the dose was changed to 1.0 gm. every four hours for four doses and subsequently reduced to 0.75 gm. every four hours until June 11. Chloramphenicol was given for the first time on the 11th day of illness and the patient became afebrile seven days later. A total of 26.25 gm. was given in 12 days. Relapses occurred on the 16th day of illness, and again on the 34th day of illness, 12 days after chloramphenicol had been discontinued the first time. A total of 91 gm. of chloramphenicol was given over a 17-day period during the second relapse. During the entire illness 117.25 gm. of the antibiotic was given. In addition to antibiotic therapy the patient received several blood transfusions and routine care for typhoid fever. The patient was discharged cured on June 24.

CASE 4: A 2½-year-old white male was admitted from the Huntington Memorial Hospital, Pasadena, to the contagious disease unit of the Los Angeles County General Hospital on May 7, 1949. He was first hospitalized on May 3 and the diagnosis of typhoid fever established by growth on a culture of the blood and by positive reaction to Widal's test. The urine was normal. A blood examination showed hemoglobin 12.4 gm. per 100 cc.; erythrocytes numbered 4,100,000, and leukocytes 5,950 with 69 per cent neutrophils. In roentgen examination of the chest, patchy bronchopneumonia at the base of the right lung was noted. The patient was given penicillin and streptomycin with no improvement. When the diagnosis of typhoid fever was established, one day before transfer to the Los Angeles County General Hospital, chloramphenicol was started, but because of vomiting the antibiotic was not retained.

The illness had begun April 26 with fever, listlessness, anorexia, vomiting and slight sore throat. The temperature remained high with late afternoon rises to 104° F. Vomiting persisted throughout the period prior to admission to the county hospital. There had been no bloody stools, diarrhea, or abdominal pain. The patient's mother and grandmother both had had typhoid fever many years ago.

Upon physical examination on May 7 the patient was noted to be acutely ill, pale, rational and oriented. The temperature was 103.8° F., the pulse rate 85, respirations 35 per minute, and the body weight 32 pounds. There were a few scattered rose spots on the abdomen. Mild bilateral conjunctivitis was present. The tonsils were enlarged and injected and there were several small ulcerated foci in the buccal mucosa of each side. The heart and lungs were normal. There was moderate distention of the abdomen. The

spleen was palpable one finger-breadth below the costal margin. The liver edge was palpable and non-tender at the costal margin.

The urine was normal. The hemoglobin content of the blood was 12 gm. per 100 cc. Leukocytes numbered 4,500 with 60 per cent neutrophils. In subsequent blood examinations these factors remained fairly constant. A culture of the blood made at the time of admission was positive for E. typhosa. Serum agglutination for E. typhosa was positive in dilution of 1:320 and negative for Para A, Para B, OX-19, and Brucella. The CO_2 combining power was 48 volumes per cent and the non-protein nitrogen 34 mg. per 100 ml. of blood. The icteric index was 7 units. The serum albumin content was 3.8 gm. and globulin content 1.6 gm. per 100 cc. Repeated cultures of catheterized urine and of stools were negative for E. typhosa.

Chloramphenicol was started May 7, two hours after admission to the hospital, with an initial dose of 0.75 gm. suspended in water, followed by 0.25 gm. every two hours until May 12, when the dose was reduced to 0.25 gm. every four hours and continued until May 17. A total of 21.5 gm. was given in 11 days. It was started on the 11th day of illness and the patient became afebrile 72 hours later. The patient showed considerable subjective improvement and was able to retain fluids and medication the day after chloramphenicol was started. A transfusion of 150 ml. of blood was given the day after admission to the hospital. Recovery was uneventful and the patient was discharged as cured on May 31.

CASE 5: A 55-year-old white female was admitted from the Huntington Memorial Hospital, Pasadena, to the contagious disease unit of the Los Angeles County General Hospital on May 19, 1949, with the diagnosis of psittacosal pneumonia. The illness had begun approximately two and a half weeks previously with anorexia, nausea, fever, frequent and painful urination, and diarrhea. Chills, cough, and abdominal pain were not noted. There was no blood in the stools. About three days before admission to the hospital dyspnea and orthopnea were noted and the patient had become "toxic" and much sicker. Aureomycin was given orally but emesis occurred. The patient's mother had had typhoid fever years previously. In the Memorial Hospital the patient was found to have a positive reaction to a Widal test in dilution of 1:640 and negative agglutinations for Para A, Para B, and Brucella. The referring physician reported significant positive complement fixation titer for psittacosis. There was moderate leukopenia and two plus albuminuria. The non-protein nitrogen was 38.5 mg. per ml. of blood. Roentgen examination of the chest revealed pneumonia in the right lung base. An electrocardiogram was normal.

Upon physical examination at the time of admission, May 19, the patient was noted to be obese, acutely ill, in a typhoid state, moderately dyspneic, dehydrated, lethargic and semi-stuporous. The facies were flushed. The temperature was 101° rectally, the pulse rate 122, the respirations 34, and the blood pressure 135 mm. of mercury systolic and 80 mm. diastolic. There were no discernible rose spots. The tongue was dry and coated, and there was a fetid oral odor. There were many fine crepitant rales at the right lung base. The abdomen was obese, soft, non-tender, with normal peristalsis apparent. The spleen was not palpable. No abnormalities were noted in a neurological examination.

On admission the hemoglobin was 13.5 gm. per 100 cc. of blood. Erythrocytes numbered 4,590,000 and leukocytes 4,700 with 62 per cent neutrophils and 38 per cent lymphocytes. These factors remained fairly constant in daily blood examinations. Agglutination was positive for E. typhosa in dilution of 1:320 and negative for Para A, Para B, OX-19, and Brucella. Result of a heterophil test was negative. On May 19 a culture of the blood was positive for E. typhosa.

Prior to admission to the Los Angeles County General Hospital the diagnostic issue had been confused by a reputed report of significantly positive complement fixation titer for psittacosis. Recovery of the typhoid organism came unexpectedly when the patient was being treated for psittacosal pneumonia. The previously reported positive complement fixation titer for psittacosis was not substantiated.

Chloramphenicol was started several hours after admission to the hospital with an initial dose of 6 gm. suspended in water divided hourly into three doses, followed by 0.50 gm. every two hours until the day of death. On that day the dose was increased to 0.75 gm. every two hours because of the grave clinical condition. A total of 31 gm. was given during the five days of hospitalization. The patient, however, retained very little of it due to intractable vomiting. Chloramphenicol was started during the third week of illness when the patient was acutely ill, and in a typhoid state. Several transfusions were given. The patient had continuous oxygen therapy and intravenous fluids. She became more stuporous and irrational, continued to vomit, and remained in a critical typhoid state. She was restless and noisy and sedation was necessary. The patient died May 23 with a terminal fever of 109° F. rectally.

CASE 6: A 15-year-old Mexican male was admitted to the Los Angeles County General Hospital July 1, 1949. Illness had begun June 26 with headache, chills, fever, nausea, vomiting, diarrhea (six loose brown colored stools daily), and general malaise.

Upon physical examination at the time of admission the patient was observed to be acutely ill; he appeared toxic and confused. The temperature was 103.6° F. rectally, the pulse rate 80, the respirations 20, the blood pressure 102 mm. of mercury systolic and 60 mm. diastolic. The weight was 135 pounds. There were no rose spots. The heart and lungs were normal. The spleen was not palpable but seemed enlarged to percussion.

The hemoglobin content was 12.5 gm. per 100 cc. of blood. Erythrocytes numbered 4,500,000 and leukocytes 4,500 with 75 per cent neutrophils. These factors remained constant in subsequent examinations of the blood. The urine was normal. Result of a Wassermann test was negative. The spinal fluid was normal. The CO_2 combining power was 67 volumes per cent and the non-protein nitrogen was 37 mg. per 100 ml. of blood. The result of a heterophil agglutination test was negative. Cultures of blood, stool, and urine were positive for Eberthella typhosa on July 1, but negative following chloramphenicol therapy. Agglutinations for E. typhosa, Para A, Para B were negative on admission.

The patient was started on aureomycin on July 3, but the drug was discontinued the following day when the diagnosis of typhoid fever was established by culture. Aureomycin had no effect on the clinical course. On July 4 the patient was transferred to the contagious disease unit of the Los Angeles County General Hospital where chloramphenicol was started with an initial dose of 1.5 gm. suspended in water, followed by 0.50 gm. every four hours for three doses, 0.50 gm. every two hours for six doses, then 0.25 gm. every two hours until July 10, when the dose was changed to 0.50 gm. every four hours until July 15. A total of 33 gm. was given in 11 days. Chloramphenicol was started on the ninth day of illness and the patient became afebrile 24 hours later. Twelve hours after the first dose and after 3.0 gm. of the antibiotic had been given, the temperature dropped precipitously to 96° F. but without clinical evidence of shock. The temperature prior to the giving of chloramphenicol ranged between 100° F. and 105° F. rectally and the patient

TABLE 1.—*Chloramphenicol Therapy*

Case No.	Day of Disease Started	Day of Disease Ended	Dosage	Total Grams	Estimation of Effect
1.	12	22	Initial dose 2.5 gm., followed by .25 gm. every 2 hours for 5 days, then .25 gm. every 4 hours.	18	Good
2.	18	26	Initial dose .75 gm., followed by .25 gm. every 2 hours for 3 days, then .25 gm. every 4 hours.	10	Good
3.	11	22	Initial dose 2.25 gm., followed by .25 gm. every 2 hours for 3 days, then .25 gm. every 4 hours for 3 more days, then .75 gm. every 4 hours.	26.25	Good
					Relapse
	35	51	Initial dose 2.25 gm., followed by .50 gm. every 2 hours for 12 days, then .75 gm. every 4 hours.	91	Good
4.	11	22	Initial dose .75 gm., followed by .25 gm. every 2 hours for 5 days, then .25 gm. every 4 hours.	21.5	Good
5.	17	22	Initial dose 2 gm., followed by 2 gm. hourly for 3 doses, then .50 gm. every 2 hours until day of death when increased to .75 gm. every 2 hours.	31 ?	Died
6.	9	20	Initial dose 1.5 gm., followed by .5 gm. every 4 hours for 3 doses, then .5 gm. every 2 hours for 6 doses, then .25 gm. every 2 hours for 6 days followed by .5 gm. every 4 hours.	33	Good

had been acutely ill and toxic. The patient made an uneventful recovery and was discharged from the hospital as cured on August 4.

DISCUSSION

The diagnosis of typhoid fever was established in all six reported cases by positive blood cultures for Eberthella typhosa prior to the administration of specific therapy. At the time of isolation of the organism, tests for in vitro sensitivity to chloramphenicol were conducted. The organism in each case was found to be sensitive to less than 0.87 micrograms per 100 ml. of blood serum.

Chloramphenicol was administered orally with varying doses because of the general lack of knowledge of the optimal dosage, starting with a minimum of 50 mg. per kilogram of body weight as the initial dose. Adequate dosage is probably proportionate to the body weight.

Chloramphenicol therapy was initiated as soon as the diagnosis was established, usually between the ninth and 18th days of illness. The mean duration of illness was 13 days; the mean duration of treatment with chloramphenicol was nine days, excluding the second relapse in one patient (Case 3).

The response of four patients to chloramphenicol therapy was prompt, three becoming afebrile in three days and the fourth in 24 hours. All patients responded subjectively to treatment within 24 to 48 hours, reduced toxicity preceding or paralleling the return of temperature to normal. Repeated blood, urine, and stool cultures were negative following the initiation of chloramphenicol therapy in these cases.

In one patient (Case 3) two febrile relapses occurred, the first while chloramphenicol was being given and the second 12 days after the antibiotic had been discontinued. The first relapse, only febrile in nature, was promptly reversed by increased dosage, the patient becoming afebrile in 12 hours. The second relapse, in which a return of bacterial growth was noted, also abated promptly when chloramphenicol was reinstituted. A blood culture taken on the day of the second relapse was positive for Eberthella typhosa. It is apparent from this case and from those reported by Woodward that complete sterilization is not always attained with chloramphenicol. The prompt response to additional treatment, however, indicates that the typhoid organism does not lose its sensitivity to the antibiotic.

The one death was not ascribable unequivocally to failure of treatment. The patient was in a typhoid state, critically ill, with pneumonia a complicating feature, and in the latter part of the third week of illness when therapy was instituted. In addition to the duration of illness before institution of therapy, very little chloramphenicol was retained due to intractable vomiting.

An interesting reaction occurred in one patient following the administration of chloramphenicol. This patient went into shock seven and a half hours after the initial dose of the antibiotic, following a precipitous drop in temperature from 103.6° F. to 95.2° F. rectally. A similar crisis in temperature occurred on two successive evenings without the accompanying manifestations of shock (Chart 1). Response of the same type occurred in one of the other patients without evidence of shock. During the prolonged course of chloramphenicol therapy one of the patients (Case 3) showed definite signs of clinical avitaminosis characterized by a red, beefy tongue and changes in the oral mucous membranes. Similar signs of avitaminosis have been observed in other patients treated with large doses of chloramphenicol. Vitamin therapy is therefore advisable in all patients receiving that antibiotic. Except for the unusual reactions noted in two patients and signs of avitaminosis in one, chloramphenicol is well tolerated.

Three patients were inadvertently given aureomycin prior to chloramphenicol therapy with no clinical improvement. The dosage and length of treatment, however, were inadequate to evaluate the efficacy of this agent. Results reported by Collins[1] and

collaborators on the use of aureomycin in the treatment of seven patients with typhoid fever are equivocal. Aureomycin did not alter the course of typhoid fever in four cases reported by Woodward;[9] two patients died following therapy. Although aureomycin has some beneficial effects, especially in vitro, the results in general are not striking. The authors' experience with aureomycin has been entirely disappointing. Two patients had nausea and vomiting following aureomycin, which interfered with subsequent chloramphenicol therapy.

It is apparent that chloramphenicol is at present the most efficacious of the available antibiotics in the treatment of typhoid fever. The optimum dosage and length of treatment are yet to be determined. It is suggested that patients in early stages of the disease respond quite dramatically to chloramphenicol, but that in advanced stages the antibiotic is less effective. The earlier treatment is instituted, the better the clinical response. Perhaps a longer period of treatment with chloramphenicol is necessary in each case if relapse is to be prevented. The observations of Smadel[5] indicate a striking relation between the duration of chloramphenicol therapy and the incidence of relapses.

REFERENCES

1. Collins, H. S., et al.: Aureomycin—a new antibiotic: Evaluation of its effects in typhoid fever, severe salmonella infections and in a case of colon bacillus bacteremia, Ann. Int. Med., 29:1077-1092, 1948.

2. Gottlieb, D., et al.: Some properties of antibiotic obtained from species of streptomyces, J. Bact., 55:409-417, March 1948.

3. J.A.M.A., 138:432, 1948: Chloromycetin (editorial).

4. McDermott, W., et al.: Chloromycetin in typhoid fever. Unpublished. Paper presented at Association of American Physicians in Atlantic City May 3, 1949.

5. Smadel, J. E., et al.: Relation of relapses in typhoid to duration of chloramphenicol therapy, J.A.M.A., 141:129, Sept. 10, 1949.

6. Smith, R. M., et al.: Chloromycetin: Biological studies, J. Bact., 55:425-448, March 1948.

7. Stiller, R.: Typhoid fever treated with chloromycetin, J. Ped., 35:85-87, July 1949.

8. Woodward, T. E., et al.: Preliminary report on the beneficial effect of chloromycetin in the treatment of typhoid fever, Ann. Int. Med., 29:131-134, 1948.

9. Woodward, T. E.: Chloromycetin and aureomycin: Therapeutic results, Ann. Int. Med., 31:53-82, 1949.

Cardiac Catheterization in Adult Congenital Heart Disease

A Preliminary Report

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SUMMARY

The diagnosis of uncomplicated ventricular septal defect and uncomplicated patent ductus arteriosus presents few hazards. Differential diagnosis of atrial septal defect and of transposed pulmonary veins is technically more difficult. The complex nature of most types of cyanotic congenital heart disease requires the combined use of catheterization, determination of circulation times, ventilation studies, and possibly angiocardiography.

Reports of eight cases in which cardiac catheterization was carried out illustrate the common forms of acyanotic and cyanotic heart disease and the factors in diagnosis.

THE purpose of this presentation is to illustrate the value of cardiac catheterization in study of congenital heart disease in adults.

MATERIAL AND METHOD

For purposes of report, eight cases of adult congenital heart disease in which catheterization was carried out at the Los Angeles County General Hospital during the years 1948 and 1949 were selected. Routine clinical work-up was followed by electrocardiography and fluoroscopy in each case. Catheterization of the heart was then carried out by the method of Cournand and co-workers.[2] Oxygen content of blood samples was measured by the Van Slyke method. The intracardiac pressures were measured by a variety of techniques including simple saline manometer, electromanometer, and by multichannel recording with strain gauge manometers.

The diagnostic value of cardiac catheterization depends primarily on the correlation of three separate kinds of information—pressure, oxygen content, and catheter position. Normal "standards" and criteria for abnormal hearts have not been universally accepted. The standards probably will change with further refinements in technique. Technical difficulties during the procedure may materially alter results. Illustrative are tachycardia induced by the "touch" effect of the tip of the catheter against the right ventricular wall, a febrile reaction during the procedure, or a change in heart rate such as may be caused by excitement. Physiologic determinations (sampling, pressures, etc.), should be made as rapidly as possible to help circumvent these problems. The technical difficulties in Van Slyke determinations and in pressure determinations appear less variable.

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I. NORMAL VALUES

1. *Atrium and Great Veins*

Normally, the superior and inferior vena cava contain blood of low oxygen content; that of the inferior vena cava is usually higher than that of the superior vena cava. Under resting conditions in the normal patient, oxygen content of superior and inferior cava blood lies between 12 and 14 volumes per cent. This presupposes the normal A-V difference of 4 to 5 volumes per cent and a normal hemoglobin content of 15 grams per 100 cc. of blood. Inferior cava blood may have oxygen content as much as 2 volumes per cent higher than does superior cava blood. This difference is presumably due to the high oxygen content of renal venous blood.

The pressure in the great veins is normally the lowest in the cardiovascular system, and varies somewhat with normal respiratory excursion. It consists of a, c, and v waves, the familiar venous pulse.

Oxygen content of right atrial blood is representative of a mixture of superior and inferior cava blood, together with the extremely unsaturated coronary sinus blood. The oxygen content of the latter is usually around 4 volumes per cent with the patient in the resting state. Right auricular oxygen content, then, may vary considerably, depending upon the proximity of the tip of the catheter to the opening of the coronary sinus, to the superior vena caval stream or to the inferior vena caval stream.

2. *Right Ventricle*

The form of the pressure wave within the right ventricle is exactly similar in contour in the normal resting state to that of the left ventricle, but the peak systolic pressure is approximately one-fourth that of the left side of the circulation, usually from 20 to 25 mm. of mercury. The form of the curve is that of an inverted "U" with rather similar ascending and descending limbs. The pressure during diastole falls to a level of 0 to 2 mm. of mercury. Oxygen content is that of a mixture of superior and inferior cava blood and blood from the coronary sinus. It may be slightly higher or slightly lower than the content in the right auricle by a difference of 1 volume per cent, depending upon the site from which the sample from the right atrium is taken.

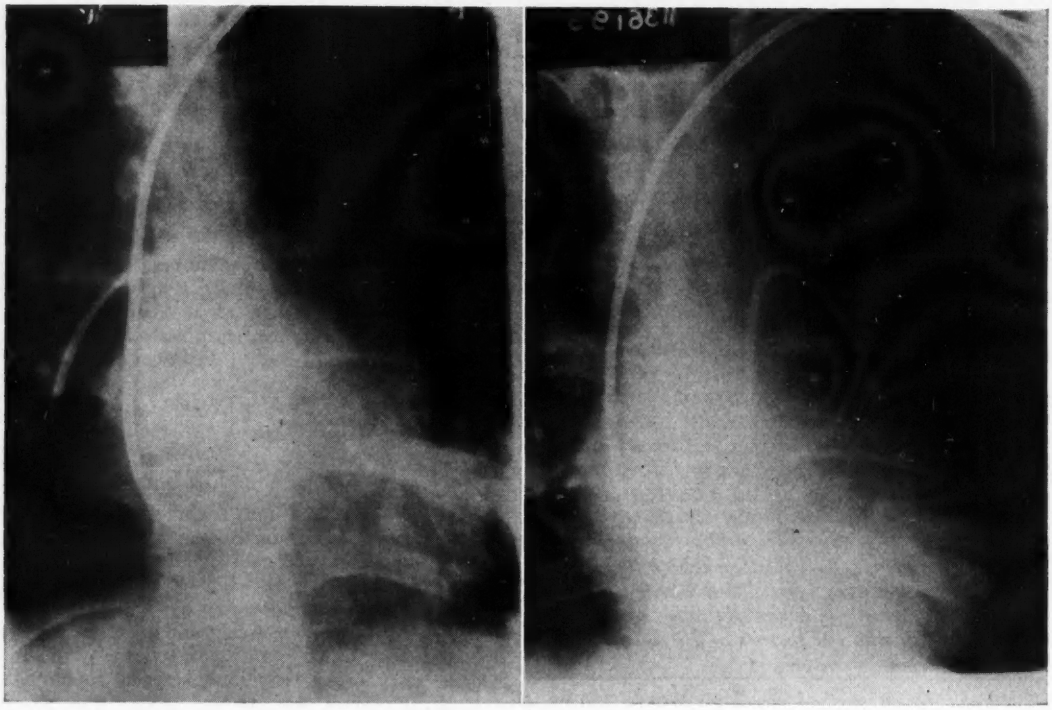

Figure 1.—*Left,* catheter in right pulmonary artery. *Right,* catheter in left pulmonary artery.

3. *Pulmonary Artery*

Normal pulmonary artery pressure curves closely resemble those of the aorta in contour and are approximately one-fourth as high in both systolic and diastolic values. Peak systolic pulmonary artery pressure always is identical to peak right ventricular systolic pressure. The oxygen content in the pulmonary artery should not vary from that of the right ventricle by more than 0.5 volumes per cent. Catheter positions in right and left pulmonary artery are illustrated in Figure 1.

However, as the catheter is passed toward the smaller pulmonary radicals, oxygenated blood appears either from collateral bronchial channels or from the pulmonary capillaries themselves. Such pure "pulmonary capillary blood" usually has oxygen content about 1 volume per cent higher than does peripheral arterial blood.[4]

II. ABNORMALITIES—ACYANOTIC CONGENITAL HEART DISEASE

1. *Transposed Pulmonary Veins*

Occasionally pulmonary veins empty directly into the superior vena cava and/or right atrium. Such an abnormality must be carefully distinguished from an atrial septal defect. Completely oxygenated blood under low, nonpulsatile pressure is present. It must be shown that the catheter has passed from superior vena cava into transposed pulmonary vein or from right atrium into transposed pulmonary vein without having passed through the left atrium.

2. *Atrial Septal Defect*

In atrial septal defect, a complete diagnosis can be made only by demonstrating passage of the catheter through the defect. Ideally, a double lumen catheter should be used and simultaneous pressure and oxygen value determinations obtained from right and left atrium. The tip of the catheter in the left atrium should record a slightly higher pressure than that in the right atrium; and from the tip in the left atrium, fully oxygenated blood is withdrawn. The proximal barrel of the double lumen catheter records the lower right atrial pressure curve and a lower "venous" oxygen content. Ordinarily, in atrial septal defect, right atrial oxygen content should be more than 2 volumes per cent above that of superior vena cava blood. It is important that the atrium be "explored" by means of multiple sampling of oxygen content.

Such data apply to isolated atrial septal defects in which the predominant shunt is from left to right. In the presence of pulmonary stenosis or other causes of right ventricular hypertrophy, where the principal intracardiac shunt is from right to left, and the tricuspid valve is incompetent, oxygen gradients may not be as striking. Superior vena cava oxygen may not differ appreciably from right atrial oxygen, and left atrial oxygen content may be lower than normal.[5]

PRESUMPTIVE INTERATRIAL SEPTAL DEFECT

CASE 1: A 27-year-old white female was referred for cardiac catheterization to confirm a diagnosis of interatrial septal defect. The growth and development of the patient had been normal. In 1943, while in the Navy, she had an attack of rheumatic fever and a heart murmur was first detected at that time.

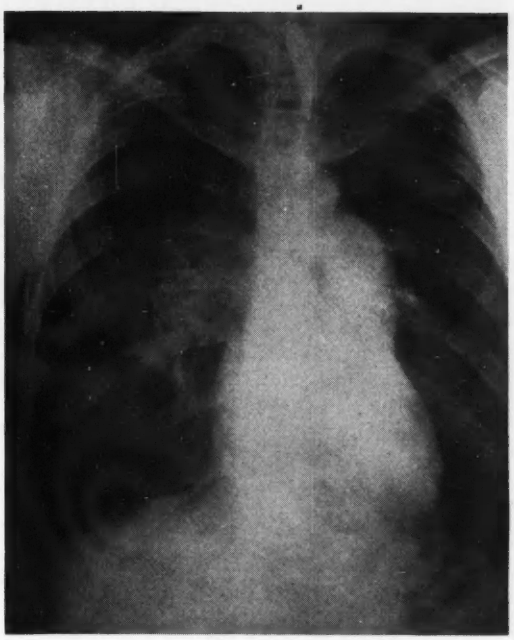

Figure 2, *A*

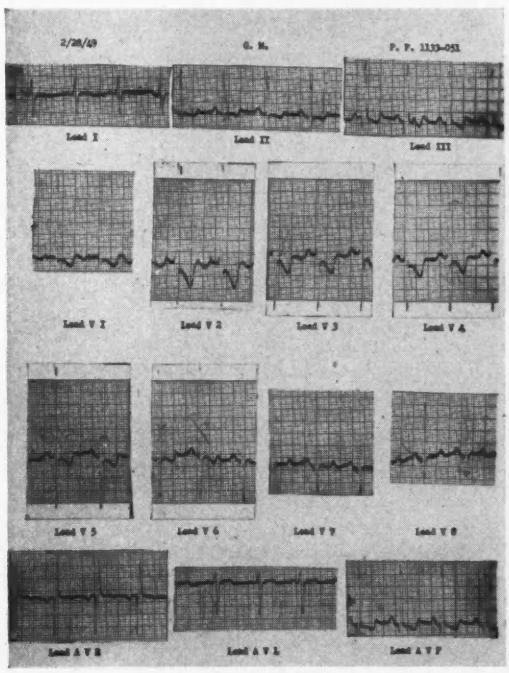

Figure 2, *B*

The patient was well developed, appeared to be well nourished and was in no acute distress. The temperature was 98.5° F., the pulse rate was 78 per minute, and the respiratory rate 20 per minute. The lungs were clear. Grade I cardiac enlargement was present. The point of maximum impulse was in the fifth intercostal space, 1 cm. outside the mid-clavicular line. P_2 and M_1 were accentuated. There was a grade V high-pitched blowing diastolic murmur, and a grade II systolic murmur at the pulmonary area.

In an orthocardiogram (Figure 2, *A*) the pulmonary arc was prominent. Pronounced dilation of the right pulmonary artery was noted in the right oblique position. The pulmonary arteries were pulsating. Right ventricular enlargement was present.

An electrocardiogram (Figure 2, *B*) gave evidence of right ventricular hypertrophy.

The hemoglobin content was 15.3 gm. per 100 cc.

Results of the cardiac catheterization are recorded in Table 1.

The diagnosis of interatrial septal defect in this patient was presumptive because of (1) an increase

TABLE 1.—*Patent Interatrial Septal Defect*

Station	Mean Pressure (mm. of Hg.)	Oxygen (Vols. %)	Oxygen Saturation (Per Cent)
1. Bifurcation of the pulmonary artery	59	14.45	69.6
2. Right ventricle	34	14.20	68.5
3. Right atrium	1 – 2	15.40	74.2
4. Superior vena cava	1 – 2	11.60	55.8
5. Left atrium	3 – 4	18.25	87.9
6. Left pulmonary vein	None	18.55	89.3

Note: With hemoglobin 15.3 gm. per 100 cc., 20.7 vol. % O_2 the saturation would be 100%.

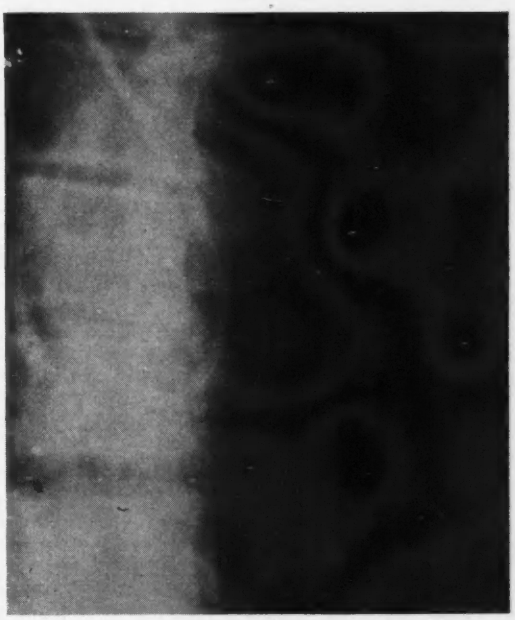

Figure 2, *C*

of oxygen content from 11.5 volumes per cent in the superior vena cava to 15.4 volumes per cent in the right auricle, and (2) because it was presumed that the catheter passed through the defect into the left auricle and out into a pulmonary vein (Figure 2, *C*). To rule out transposed pulmonary vein would have necessitated simultaneous pressure and oxygen recordings with the double lumen catheter in two positions, right atrium-left atrium, and left atrium-pulmonary vein.

3. *Ventricular Septal Defect*

An increase in oxygen content of greater than 1 volume per cent between right atrium and right ventricle is indicative of ventricular septal defect. The ventricular pressure and oxygen content depend upon (1) the size of the defect present, and (2) the proximity of the catheter to the defect itself. Occasionally the tip of the catheter may be passed through the defect, and left ventricular pressure curves may be recorded together with the sampling of fully oxygenated blood.

HIGH INTERVENTRICULAR SEPTAL DEFECT

CASE 2: A 21-year-old Japanese-American female with a history of heart disease since birth was admitted for cardiac catheterization. The only complaint was of dyspnea on exertion.

The patient was underweight. There was no dyspnea, orthopnea, cyanosis or clubbing. The pulse rate was 72 per minute. The blood pressure was 110 mm. of mercury systolic and 70 mm. diastolic. The lungs were clear. In examination of the heart the point of maximum intensity was noted in the fifth interspace at the anterior axillary line. There was a prominent systolic thrill at the second and third intercostal spaces to the left of the sternum. A grade IV systolic murmur was heard at the pulmonic area and it was transmitted to the left clavicle. A grade II pulmonary diastolic murmur was also present. P_2 was accentuated.

An orthocardiogram (Figure 3, *A*) showed that the vascular markings in both lung fields were increased, and that pronounced pulsations of the pulmonary arteries were present. The pulmonary arc was prominent. In the left oblique, both right and left ventricles were enlarged and there was a small right atrial shelf. In the right oblique the left atrium was enlarged.

An electrocardiogram showed right axis deviation (Figure 3, *B*).

Prior to catheterization, this patient was thought to have either an interatrial septal defect or a high interventricular septal defect. The results of the cardiac catheterization are recorded in Table 2.

The oxygen content of the blood in the right ventricle was approximately 2 volumes per cent higher than that of the right atrium. This established a diagnosis of interventricular septal defect. The fact

TABLE 2.—*Interventricular Septal Defect*

Station	Oxygen Content (Vols. %)	Mean Pressure (mm. of Mercury)
1. Coronary sinus	4.30	9
2. Pulmonary conus	15.70	30
3. Right ventricle	15.80	41
4. Right atrium	13.70	0
5. Superior vena cava	12.90	0
6. Femoral artery	17.45	—

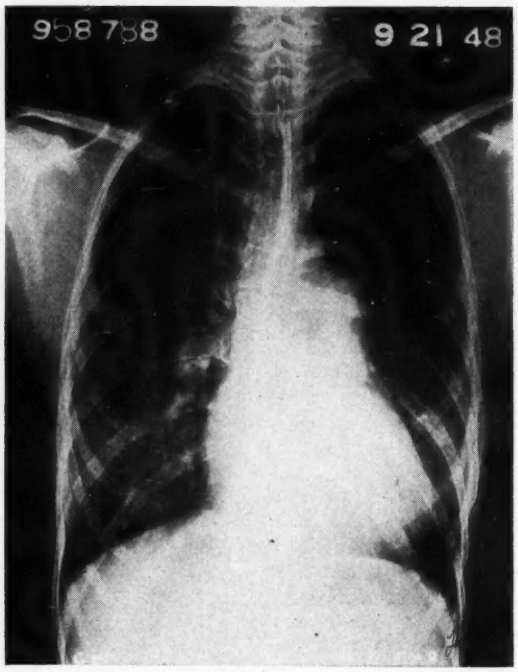

Figure 3, *A*

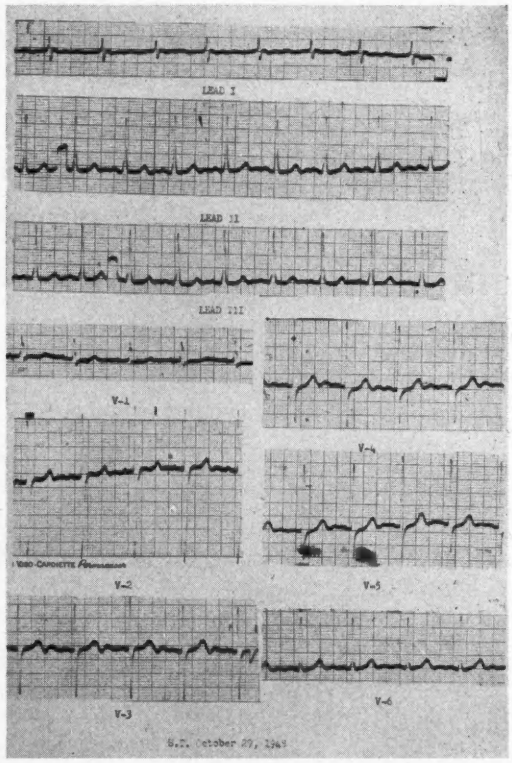

Figure 3, *B*

Figure 3, *C*

that the oxygen content of the blood in the right atrium was 0.8 volume per cent higher than that of the superior vena cava could possibly represent a very small interatrial septal defect. The catheter was fortuitously passed into the coronary sinus (Figure 3, *C*), and there the oxygen content was 4.3 volumes per cent. The increase in pressure in the right ventricle was secondary to the pulmonary hypertension.

4. *Patent Ductus Arteriosus*

An increase in oxygen content greater than 0.5 volume per cent between right ventricle and main pulmonary artery is indicative of some type of aortic-pulmonary shunt, usually patent ductus arteriosus. It also may be indicative of a shunt between left ventricle and pulmonary artery (high intraventricular septal defect, either alone or in combination with other defects). The actual form of the pressure curve and the degree of increase of oxygen content depends, as in ventricular septal defect, upon the size of the defect and the proximity of the catheter tip.

CASE 3: A 32-year-old white female with a history of heart disease was referred for cardiac catheterization to confirm the diagnosis of patent ductus arteriosus. The growth and development of the patient had been normal.

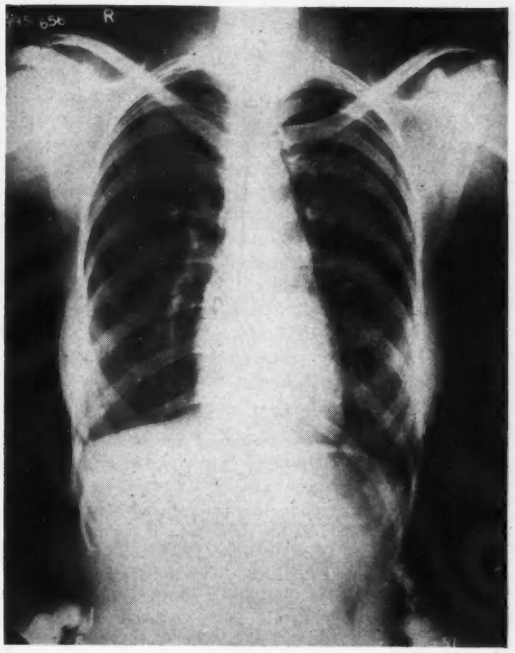

Figure 4

TABLE 3.—*Patent Ductus Arteriosus*

Station	Oxygen Content (Vols. %)	Mean Pressure (mm. of Mercury)
1. Right pulmonary artery	16	25
2. Bifurcation of main pulmonary artery	16.05	29
3. Right ventricle	14.04	16
4. Right atrium	14.5	7

The patient was thin and underdeveloped. There was no dyspnea, cyanosis or clubbing. The pulse rate was 72 per minute. The blood pressure was 115 mm. of mercury systolic and 60 mm. diastolic. The lungs were clear. A continuous "machinery" murmur over the pulmonic area was noted in examination of the heart.

An orthocardiogram (Figure 4) showed increased vascular markings, and the pulmonary arteries were described as pulsating. The heart was of normal size, and the pulmonary conus was prominent.

An electrocardiogram was normal. The hemoglobin content was 17.6 gm. per 100 cc. of blood. Results of cardiac catheterization are recorded in Table 3.

In this case, the oxygen content of the blood taken from the pulmonary artery was significantly higher (2 volumes per cent) than that in the right ventricle. This confirmed the diagnosis of patent ductus arteriosus. It is to be noted again that position of the tip of the catheter determines the oxygen and pressure values, and that the optimum position is at or near the bifurcation of the pulmonary artery. Calculation of the size of any left-to-right shunt by the usual methods may vary considerably depending upon the location of the catheter tip.[2]

5. *Isolated Pulmonary Stenosis (Non-Cyanotic)*

The diagnosis of pulmonary stenosis rests upon the finding of an abrupt rise of pulmonary systolic pressure during withdrawal of the catheter through the pulmonary valve. Ordinarily in this abnormality the pulmonary artery systolic pressure will be below 25 mm. of mercury, and the right ventricular systolic pressure considerably above that level. The diagnosis is reasonably accurate, since, under normal conditions, the systolic pressure in both pulmonary artery and right ventricle is identical. Oxygen saturation in isolated pulmonary stenosis is usually within the normal range in the peripheral arterial circulation, as the blood passing through the lungs is completely oxygenated, and there are no right-to-left intracardiac shunts.

CASE 4: A 25-year-old Negro female with a history of dyspnea on exertion since childhood and ankle edema for the previous 12 months was admitted for cardiac catheterization.

The patient appeared to be in no acute distress. The temperature was 98.6° F., the pulse rate 82 per minute, and the respiratory rate 18 per minute. The blood pressure was 132 mm. of mercury systolic and 94 mm. diastolic. The neck veins were pulsating. The lungs were clear. Grade II cardiac enlargement was present. The point of maximum intensity was in the fifth intercostal space, 3 cm. outside the midclavicular line. P_2 was accentuated. There was a grade III systolic murmur at the pulmonic area transmitted toward the left clavicle. The liver, which was palpated three fingers' breadth beneath the right costal margin, pulsated.

An orthocardiogram (Figure 5, *A*) showed marked cardiac enlargement, chiefly right ventricular, with a prominent pulmonary arc. The pulmonary vascular markings were considerably diminished.

An electrocardiogram gave evidence of right ventricular hypertrophy (Figure 5, *B*).

Erythrocytes numbered 5.5 million, and the hemoglobin content was 17 gm. per 100 cc. The results of cardiac catheterization are recorded in Table 4.

The catheter could not be passed into the pulmonary artery. The finding of a pressure of 97 mm. of mercury in the right ventricle was consistent with the clinical and roentgenologic impression of pure pulmonary stenosis. The inability to introduce the catheter through the pulmonary valve was an additional suggestive finding. The presence of 91 per cent oxygen saturation in the femoral artery indicated complete oxygenation of pulmonary blood, and the absence of a right-to-left intracardiac shunt. These three findings—(1) starved lungs, with high right ventricular pressure, (2) the inability of the catheter to enter the pulmonary artery and (3) normal arterial oxygen saturation—established the presumptive diagnosis of pure pulmonary stenosis. Illustrative cases of pulmonary stenosis with *diagnostic* pressure gradients from right ventricle to pulmonary artery will be reported later in this presentation (Cases 5 and 6).

TABLE 4.—*Pure Pulmonary Stenosis*

Station	Mean Pressure (mm. of Hg.)	Oxygen (Vols. %)	Oxygen Saturation (Per Cent)
1. Right ventricle	97	10.37	49.1
2. Right atrium	19	9.99	48.8
3. Subclavian vein	19	9.97	46.7
4. Femoral artery		18.8	91.7

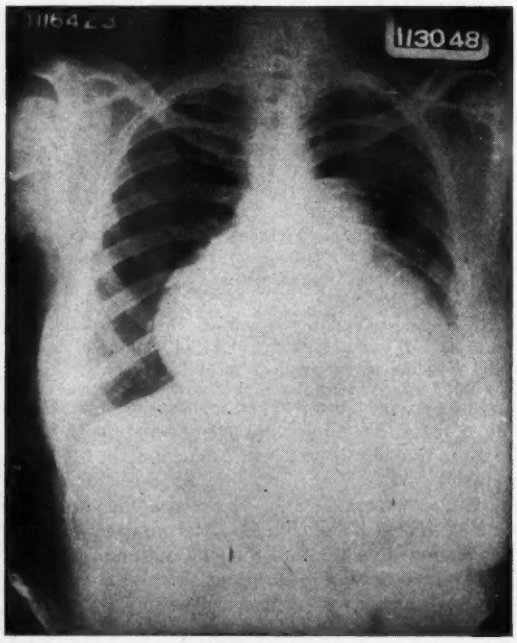

Figure 5, *A*

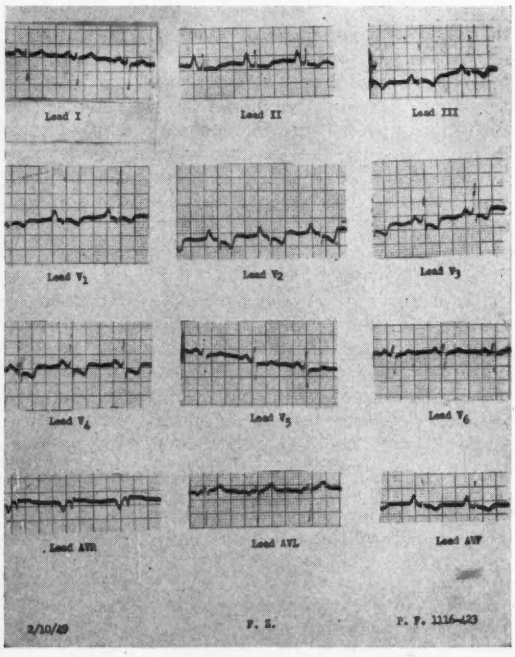

Figure 5, *B*

III. CYANOTIC CONGENITAL HEART DISEASE

1. *Tetralogy of Fallot*

The tetralogy of Fallot is the commonest type of cyanotic congenital heart disease and consists of (1) an interventricular septal defect, (2) dextroposition of the aorta, (3) right ventricular hypertrophy and (4) pulmonary stenosis.

It is not always possible, with the technique of cardiac catheterization, to arrive at a "complete" physiologic diagnosis. Nevertheless, significant and valuable information is almost invariably obtained. The data may be subdivided thus:

1. *Pulmonary stenosis.* This is the crucial determination, and, as was noted earlier, is determined best by the rise of systolic pressure during continuous withdrawal of the catheter from pulmonary artery to right ventricle. In addition, information may be gathered as to the actual presence of one or both pulmonary arteries, provided that the catheter is manipulated into the terminal portion of each pulmonary artery.

2. *Hypertrophy of the right ventricle.* This is a result of pulmonary stenosis and is evidenced by (a) elevated right ventricular systolic pressure, (b) right axis deviation with evidence of hypertrophy in the electrocardiogram, and (c) fluoroscopic demonstration of right ventricular enlargement.

3. *Dextroposition, or overriding aorta.* Four methods are available to demonstrate overriding: (a) arm-to-tongue circulation time (approximates arm-to-lung time), (b) angiocardiography will reveal the early presence of dye in the aorta when it can be definitely proven that dye has passed directly from right atrium to right ventricle to aorta, (c) the catheter itself may be seen to pass from apparent right ventricle to aorta, (d) a right ventricular systolic pressure equal to aortic systolic pressure is fairly good evidence for the presence of overriding. It is apparent that no one of the above methods is infallible, and all should be utilized during cardiac catheterization.

4. *Interventricular septal defect.* This defect in cyanotic heart disease is not simple to demonstrate by the technique of catheterization, since the shunt may be mainly from right to left. This septal defect may be assumed to be present when overriding of the aorta is demonstrated.

The differentiation of tetralogy of Fallot from the tetralogy of Eisenmenger requires, in addition, the determination of oxygen consumed per liter of ventilation and the determination of changes in arterial oxygen saturation with exercise. In the tetralogy of Fallot the arterial oxygen saturation falls with exercise, as does oxygen consumed per liter of ventilation.[1] In the tetralogy of Eisenmenger the arterial oxygen saturation falls with exercise, and the oxygen consumption per liter of ventilation rises.

CASE 5: A 21-year-old white male with a history of cyanosis and clubbing since four years of age was admitted for cardiac catheterization. The only complaint was that of dyspnea on moderate exertion.

The patient was moderately underdeveloped. Pronounced cyanosis of the skin and mucous membranes was noted. There was clubbing of the fingers, toes, and nose. The temperature was 98° F., the pulse rate 120 per minute and the respiratory rate 20 per minute. The blood pressure in the right arm was 118 mm. of mercury systolic and 90 mm. diastolic; in the left arm, 115 mm. systolic and 100 diastolic. The lungs were clear. There was a harsh grade III systolic murmur best heard over the third and fourth left interspaces and transmitted well in all directions. P_2 was louder than A_2.

An orthocardiogram showed some decrease in the peripheral lung markings. The cardiac silhouette was not enlarged. In the right oblique the pulmonary artery appeared quite small (Figure 6, *A*).

An electrocardiogram gave evidence of right axis deviation with pronounced clockwise rotation of the heart (Figure 6, *B*).

The hemoglobin content of the blood was 23 gm. per 100 cc. Erythrocytes numbered 8.5 million, and leukocytes 7,600.

The results of cardiac catheterization are recorded in Table 5. In Figure 6, *C* there are simultaneous pressure

TABLE 5.—*Tetralogy of Fallot*

Station	Oxygen Content (Vols. %)	Oxygen Saturation (Per Cent)	Pressure (mm. of Hg.) Systolic	Diastolic
1. Main pulmonary artery	17.54	48.5	25 to 33	18 to 21
2. Right ventricle *High*	18.7	51.7	155 to 167	28 to 32
2. Right ventricle *Low*	17.80	49.3		
3. Right atrium	17.65	48.8	15 to 20	5 to 10
4. Superior vena cava	19.88	55	15 to 20	5 to 10
5. Left brachial artery	25.85	71.6	90	75

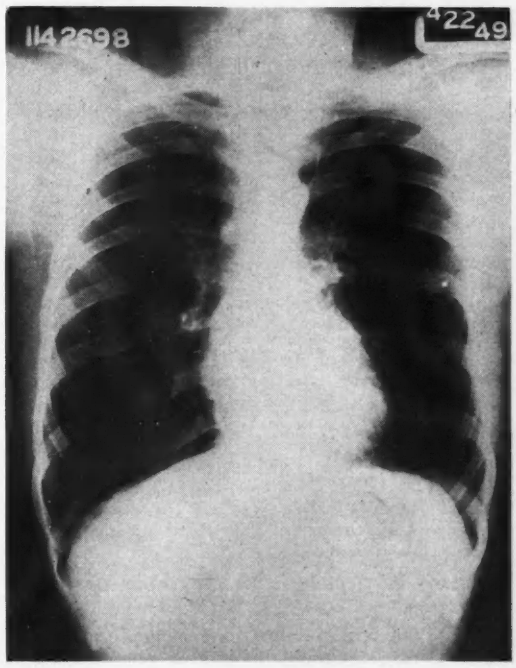

Figure 6, *A*

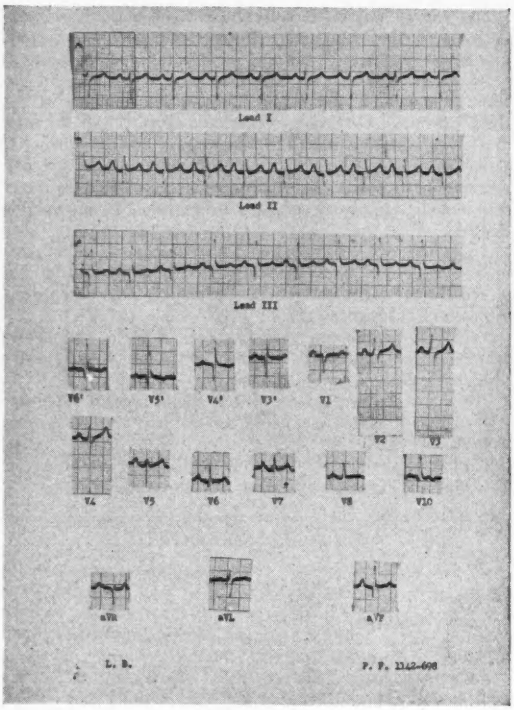

Figure 6, *B*

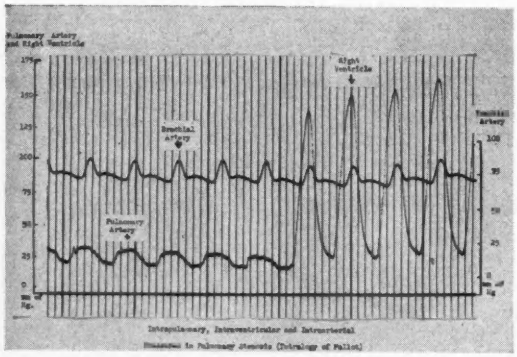

Figure 6, *C*

recordings from the catheter and an intra-arterial needle. The pronounced rise in pressure (Figure 6, *C*) as the catheter was withdrawn from the pulmonary artery into the right ventricle was objective proof of the presence of pulmonary stenosis. The rise of oxygen high in the right ventricle was possible evidence of a high interventricular septal defect. The very high right ventricular systolic pressure suggested overriding of the aorta and implied that the predominant shunt was from right to left. The diagnosis arrived at was that of tetralogy of Fallot, and a Blalock-Taussig operation was advised.

2. *Interatrial Septal Defect Plus Pulmonary Stenosis*

In the differential diagnosis of cyanotic congenital heart disease, pulmonary stenosis plus interatrial septal defect holds an important place. Operative results in this condition have been equivocal in spite of the presence of pulmonary stenosis and pronounced subnormality of oxygen content in arterial blood. To demonstrate the interatrial septal defect, the oxygen content of superior and inferior caval blood is a matter of great importance. The dynamics of the interatrial defect include shunts from right to left and from left to right. Ideally, the catheter should be passed through the interatrial defect into the left atrium.

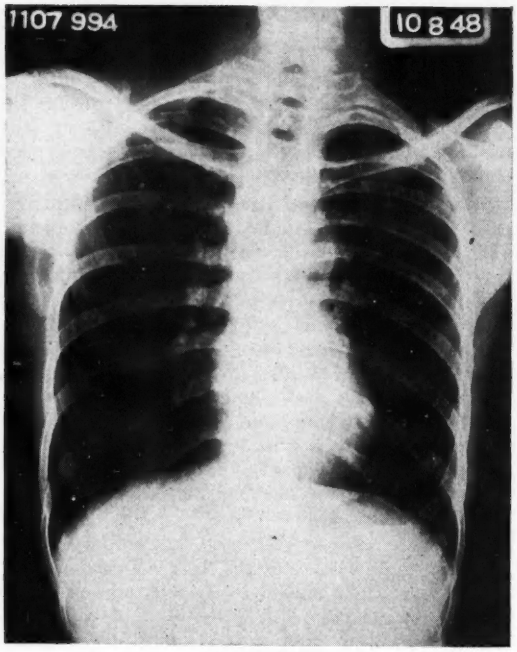

Figure 7, *A*

CASE 6: A 23-year-old white male, cyanotic since birth, who complained of dyspnea and increase of cyanosis on exertion, was admitted for cardiac catheterization. He had frequently assumed a "squatting" position in the past. Growth and development had been somewhat impaired.

Upon physical examination, clubbing of fingers and toes was noted. The pulse rate was 66 per minute. The blood pressure was 95 mm. of mercury systolic and 70 mm. diastolic. The lungs were clear. The heart was not enlarged. There was a systolic thrill at the second and third interspaces to the left of the sternum. A grade IV systolic murmur was present at the second, third and fourth intercostal spaces to the left of the sternum and was transmitted into the neck.

An orthocardiogram showed some decrease in the vascular markings in the periphery of the lung fields (Figure 7, *A*). The heart was small and there was no concavity in the region of the pulmonary arc. In the left oblique, the right ventricle appeared to make up at least two-thirds of the cardiac silhouette.

An electrocardiogram gave evidence of right ventricular hypertrophy (Figure 7, *B*).

The hemoglobin content of the blood was 27.5 gm. per 100 cc. The results of cardiac catheterization are recorded in Table 6.

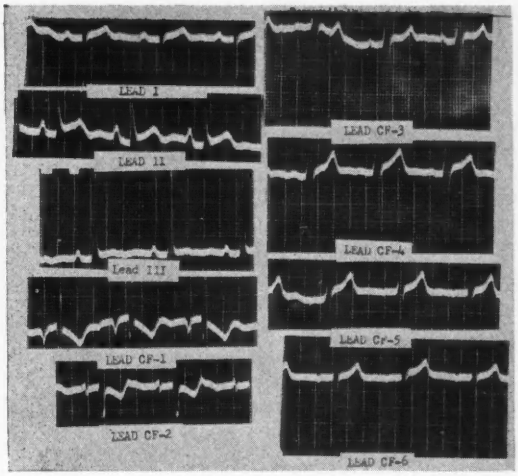

Figure 7, *B*

TABLE 6.—*Pulmonary Stenosis with Either an Interatrial Septal Defect or Transposed Pulmonary Veins*

Station	Oxygen Content (Vols. %)	Oxygen Saturation (Per Cent)	Mean Pressure (mm. of Mercury)
1. Right pulmonary artery	21.7	58.5	2 – 3
2. Right ventricle	22.1	59.6	39 – 61
3. Right atrium	22.1	59.6	1 – 2
4. Superior vena cava	18.5	50.0	0
5. Femoral artery	25	63.8	—

Note: With hemoglobin content at 27.5 gm. per 100 cc., 37.04 volumes % of oxygen would be needed for 100% saturation.

The oxygen content of the right atrium was 3.6 volumes per cent higher than that of the superior vena cava, representing either interatrial septal defect or transposed pulmonary veins. Also, the pressure, which was elevated in the right ventricle (39 to 61 mm. of mercury), dropped to 3 to 4 mm. in the pulmonary artery. From these data, the diagnosis of pulmonary stenosis was proven.

3. *Tetralogy of Eisenmenger*

The main diagnostic differential from tetralogy of Fallot is the tetralogy of Eisenmenger in which is found (1) a high interventricular septal defect, (2) right ventricular hypertrophy, (3) dextroposition of the aorta and (4) a *normal* or *dilated* pulmonary artery. Cyanosis usually does not appear until about the age of puberty.

In the complex of Eisenmenger, the following determinations should pertain: (1) identical and simultaneous systolic pressure in pulmonary artery and right ventricle (both elevated above the normal, usually by a considerable amount). Both should be identical, or very nearly identical with that of aortic systolic pressure. (2) Right ventricular hypertrophy is self-evident in the above. (3) The interventricular septal defect is more often evident than in the tetralogy of Fallot, and thus, right ventricular oxygen content tends to be higher than right

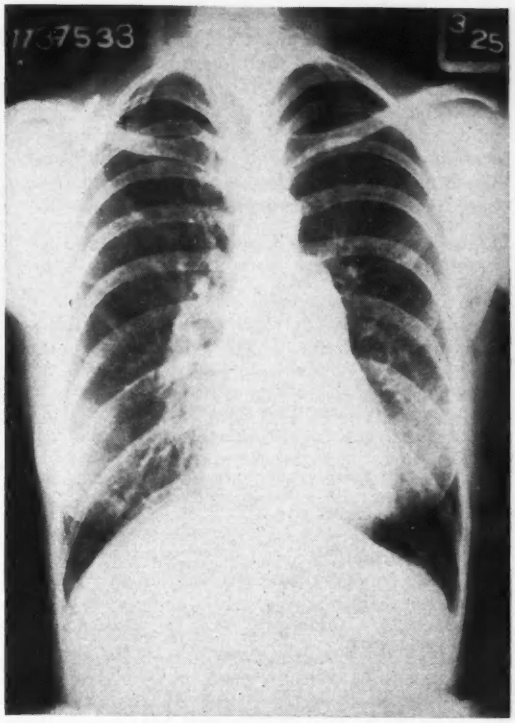

Figure 8, *A*

atrial oxygen content. (4) Finally, although there is a fall of arterial oxygen saturation with exercise as in the tetralogy of Fallot, the oxygen consumed per liter of ventilation rises.

CASE 7: A 29-year-old white female, cyanotic since age 13, was admitted for cardiac catheterization. The cyanosis had persisted since onset, and clubbing of the fingers and toes had developed. Dyspnea occurred only on severe exertion.

Upon physical examination, cyanosis of the skin and mucous membranes was noted. Clubbing of fingers and toes was present. The temperature was 99° F., the pulse rate was 84 per minute, and the respiratory rate was 18 per minute. The blood pressure was 100 mm. of mercury systolic and 78 mm. diastolic. The lungs were clear. The heart was not enlarged on percussion. The point of maximum intensity was in the fifth intercostal space at the midclavicular line. P_2 was louder than A_2. There was a grade II systolic murmur at the base, best heard over the pulmonic area, and transmitted into the neck and toward the apex.

An orthocardiogram showed increased pulmonary markings with pulsating pulmonary arteries. Grade II right ventricular enlargement was present (Figure 8, *A*). An electrocardiogram gave evidence of right ventricular hypertrophy (Figure 8, *B*). Hemoglobin content of the blood was 19.5 gm. per 100 cc. Leukocytes numbered 7,700. The arm-to-tongue circulation time (dehydrocholic acid) was 12 seconds, and the arm-to-lung circulation time (ether) was 8 seconds.

The results of cardiac catheterization are recorded in Table 7, and the pressure readings are recorded in Figure 8, *C*.

The pressure in the main pulmonary artery was 102 mm. of mercury systolic and 50 mm. diastolic; pressure in the right ventricle was 99 mm. systolic

and 2 mm. diastolic. The following measurements were pertinent and typical: (1) The right ventricular systolic pressure, and the pulmonary artery systolic pressure were considerably elevated and similar. (2) The pressures in both approximated the brachial artery systolic pressure. (3) The high oxygen content of pulmonary artery was presumably caused by a high interventricular septal defect. The findings were typical of Eisenmenger's complex.

4. *Rudimentary Right Ventricle and Transposed Pulmonary Veins*

In cyanotic congenital heart disease, right axis deviation is definitely more common than left axis deviation. The finding of left axis deviation usually suggests a small or rudimentary right ventricle, often with the added feature of tricuspid atresia. (Left axis deviation may also occur in single ventricle or with a tetralogy of Fallot with dextrocardia.) The following case illustrates these features and, in addition, the presence of pulmonary veins entering the right atrium.

TABLE 7.—*Tetralogy of Eisenmenger*

Station	Oxygen Content (Vols. %)	Oxygen Saturation (Per Cent)	Pressure Syst./Diast. (mm. Hg.)	Pressure Mean
1. Right pulmonary artery	17.8	76.5	115/50	78–82
2. Main pulmonary artery	17.6	70.6	102/50	78–80
3. Right ventricle	16.0	60.6	99/2	43–60
4. Right atrium	15.5	58.8	6/2	2–4
5. Superior vena cava	14.7	55.7		
6. Right brachial artery	21.8	82.7	115/75	95

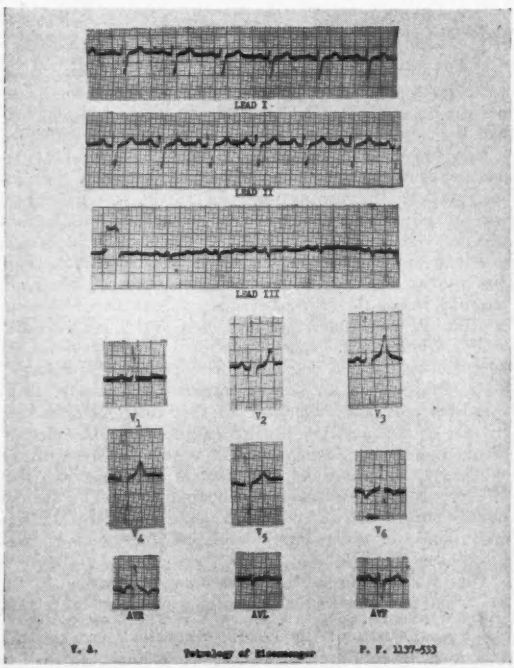

Figure 8, *B*

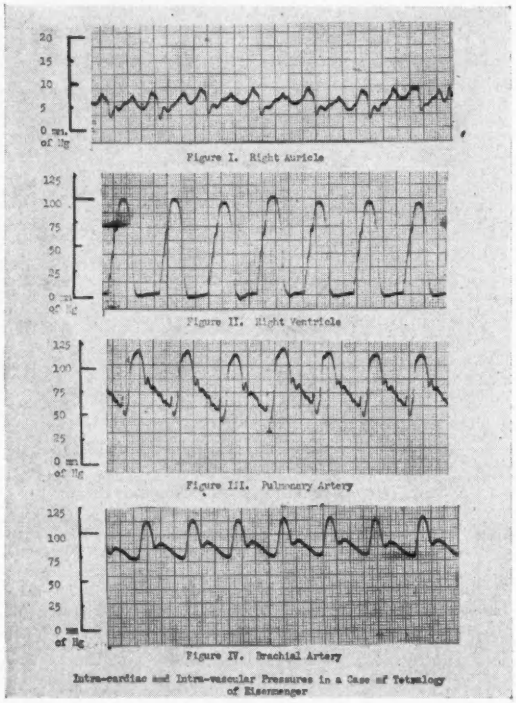

Figure 8, *C*

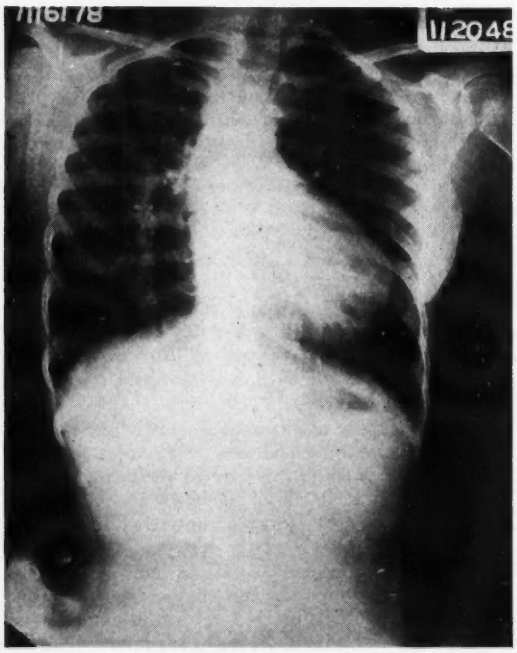

Figure 9, *A*

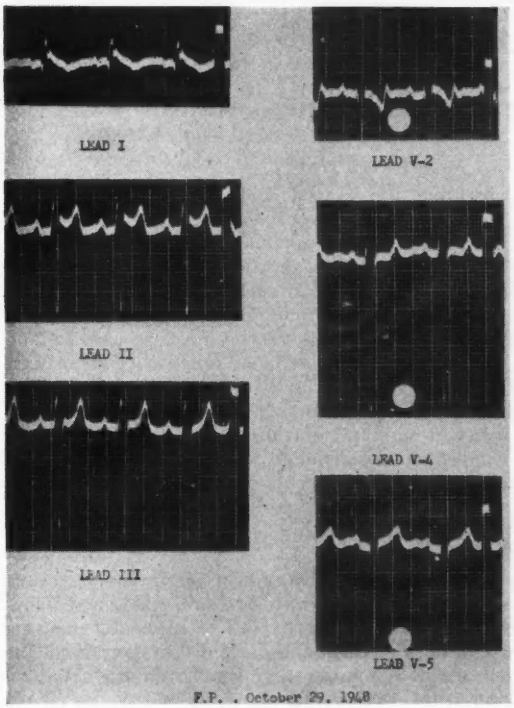

Figure 9, *B*

CASE 8: A 13-year-old white female, a "blue baby," and cyanotic since birth, was admitted to the Los Angeles County Hospital on November 20, 1948, for cardiac catheterization. Growth and development had been normal, but the exercise tolerance had been low as long as the patient could remember.

The patient was well developed. Cyanosis and clubbing of fingers and toes were present. The blood pressure was 94 mm. of mercury systolic and 88 mm. diastolic. The lungs were clear. Upon examination of the heart the point of maximum intensity was located in the fifth intercostal space at the midclavicular line. P_2 was accentuated and greater than A_2. There was a grade III systolic murmur in the fifth interspace just inside the midclavicular line.

An orthocardiogram (Figure 9, *A*) showed a boot-shaped left ventricle in the posterior-anterior view. One plus enlargement was present. In the left oblique view there was a straightening of the normal contour of the right ventricle which suggested a small or non-functioning right ventricle.

An electrocardiogram gave evidence of pronounced left axis deviation. The QRS interval was prolonged (Figure 9, *B*).

The results of cardiac catheterization are recorded in Table 8. Prior to catheterization, the main features of this case were: (1) cyanotic heart disease with left axis deviation and (2) an orthocardiogram showing a small or rudimentary right ventricle.

TABLE 8.—*Rudimentary Right Ventricle with Transposition of the Pulmonary Veins*

Station	Oxygen Content (Vols. %)	Oxygen Saturation (Per Cent)	Mean Pressure (mm. of Mercury)
1. Right pulmonary vein	24.5	80.0	9
2. Coronary sinus	4.45	14.5	40
3. Right atrium	16.8	53.4	18
4. Superior vena cava	14.7	46.8	9
5. Aorta	20.4	65.3	40

During the catheterization, the catheter was first observed to pass directly from the superior vena cava and the right atrium into the right pulmonary vein, from which oxygenated blood was obtained. Later, the catheter was passed into the aorta (presumably from right ventricle, through interventricular septal defect, into left ventricle) and appeared in the descending aorta at about the level of the second lumbar vertebra.

Reviewing all the findings, the following defects were established: (1) transposed pulmonary veins (by the presence of completely oxygenated blood in a vein emptying into the superior vena cava); (2) rudimentary or nonfunctioning right ventricle (straight anterior margin of the heart in the left oblique position by x-ray and the extreme left axis deviation in the electrocardiogram. It is presumed (but not proven) that interatrial septal defect, with or without interventricular septal defect, completes the picture in this malformation.

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REFERENCES

1. Bing, R. J., Handelsman, J. C., and Campbell, J. A.: Physiologic diagnostic tests in congenital heart disease, Modern Concepts Cardiovas. Disease, 17: [n.p.], March 1948.

2. Cournand, A., Baldwin, J. S., and Himmelstein, A.: Cardiac Catheterization in Congenital Heart Disease. Commonwealth Fund. New York City. 1949.

3. Cournand, A., and Ranges, H. A.: Catheterization of right auricle in man, Proc. Soc. Exp. Biol. and Med., 46:462, March 1941.

4. Dexter, L., Haynes, F., Burwell, C., Eppinger, E., Sagerson, R., and Evans, J.: Studies of congenital heart disease. II. The pressure and oxygen content of blood in the right auricle, right ventricle and pulmonary artery in control patients, with observations on the oxygen saturation and source of pulmonary "capillary" blood, J. Clin. Investigation, 26:554, 1947.

5. Vandam, L. V., Bing, R. J., and Gray, F. D., Jr.: Physiological studies in congenital heart disease. IV. Measurements of the circulation in five selected cases, Bull. J. Hopkins Hosp., 81:192, Sept. 1947.

Habitual Abortion

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SUMMARY

Habitual abortion should be defined as the spontaneous sequential loss of three or more pre-viable pregnancies.

The incidence and etiology of spontaneous single and repeated, sequential abortion are discussed.

The theoretical role of the various hormones in the treatment of abortion is examined.

The modes of therapy now in effect are reviewed and their probable value estimated.

Preconceptual therapy of the wife and husband for the successful salvage of a viable infant following previous sequential abortion is recommended.

Logical postconceptual and emergency therapy is outlined for the patient who is an habitual aborter.

A critical view of previous and present methods of study and treatment of habitual abortion is expressed.

HABITUAL abortion is a challenge to the obstetrician because of the complexity of causes and the low salvage achieved thus far with any or all of the available therapeutic regimens. Undue pessimism has characterized the attitude of both the layman and the physician regarding the outcome of subsequent pregnancies in patients who have had repeated abortion. On the other hand, there has been unjustified optimism regarding hormone therapy. These conflicting opinions have confused obstetrical thought. This review is intended to define habitual abortion, to summarize current thought concerning some of the factors involved in repetitious abortion, and to evaluate the therapy of this malady.

Habitual abortion has been variously defined. The sequential loss of three or more pre-viable pregnancies seems to be the most acceptable definition.[6,16,17] An elaboration of this definition suggests that patients who have had three or more consecutive abortions, beginning with the first pregnancy, be considered as primary habitual aborters. The term "secondary habitual abortion" would then be applied to those patients who have had three or more consecutive abortions following delivery of one or more premature or full-term infants.[13] However, not all observers are agreed upon these interpretations. Some clinicians have professed to consider the term "habitual aborter" applicable to women who have had more than one abortion,[10] two or more abortions,[9] abortions occurring repeatedly,[26] or, abortions in a number of successive pregnancies.[25] Chronic abortion has also been a term used to indicate repeated, although not necessarily sequential, abortion.[23] Such a variety of definitions represents a multiplicity of impressions regarding the incidence of habitual abortion. Add to this situation the complexity of compound therapy and the subject of habitual abortion becomes completely chaotic. The satisfactory comparison of one series of sequential abortions with another is therefore almost impossible.

Another point of argument is: How small must an infant be to be considered non-viable and therefore its birth as abortive? The successful management of the premature infant has permitted the salvage of numerous very small infants during recent years. Most of the reports of salvage have come from the larger hospitals or medical centers. For example, Levine has reviewed the survival of 32 infants weighing between 501 and 1,000 gm. in recent years.[13] It may be that the classification of infants should be scaled below the usually accepted limit of 1,501 gm. as a minimal weight for a viable child. However, the survival of infants weighing less than 1,500 gm. is rare. For the time being, therefore, the original concept that infants below 1,500 gm. will probably not survive will be adhered to. This point of view applies in vital statistics and is generally retained in most articles on sequential abortion.

INCIDENCE OF SPONTANEOUS ABORTION

The incidence of spontaneous abortion in general is between 10 per cent and 20 per cent of all pregnancies.[9,15,27] Sequential or habitual abortion constitutes about 0.4 per cent of all pregnancies or 4 per cent of all spontaneous abortions.[6] The women in whom such abortions occur are not sterile in the true sense of the word, but since they cannot carry a fertilized ovum to maturity or viability, they have "pseudo-sterility."[22] Javert reported the incidence of primary habitual abortion as 0.3 per cent and of secondary habitual abortion as 0.2 per cent of all pregnancies.[13] Full term expectancy is probably somewhat better in the secondary group.

All spontaneous abortions occur because of (1) random or accidental factors which are usually not repetitious, and (2) recurrent or persistent factors. Random factors are unlikely to recur save by chance. Recurrent factors, on the other hand, are

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due to inherent conditions which are inimical to the growth and maturity of the ovum in each successive pregnancy. If 10 per cent is accepted as an average figure for the incidence of spontaneous abortion in all pregnancies, it has been calculated that 0.4 per cent of these terminate because of recurrent factors. Malpas,[16, 17] and more recently Eastman,[6] have calculated the incidence of abortion factors. They have found that a definite spontaneous cure rate is to be expected despite one, two or more spontaneous abortions.

Not all embryologists agree upon 10 per cent as the correct incidence of spontaneous abortion. Certain investigators have placed the figure much higher—some to 20 per cent.[10, 27] For this reason, the author has calculated (Table 1) the spontaneous cure rate following repeated abortion, after the method of Eastman,[6] on the basis of 10 per cent *and* 20 per cent abortion incidence. It is apparent that after three or more abortions, the percentage of spontaneous cure is somewhat higher with the 20 per cent figure. (Actually, the true figure may be somewhere between 10 per cent and 20 per cent.)

TABLE 1.—*Chances of Repeat Abortion in Successive Pregnancies if One Assumes a 10 Per Cent vs. 20 Per Cent Incidence*

Previous Abortions	Per Cent Will Abort	Spontaneous Cure Rate 20% Incidence	10% (Eastman)
0	20.0	.....	.....
1	22.4	77.8%	86.8%
2	33.6	66.4	63.1
3	68.3	31.7	16.4
4	88.2	11.8	0.1

It will be concluded, then, that the physician is justified in assuming a fairly optimistic prognosis for a third pregnancy in women who have had two or more spontaneous abortions. It is apparent that previous abortion is not a grave damper on expectation of successful pregnancy until after three or more sequential abortions. For the same reasons the doctor should be extremely critical of the value of medication given a patient in a third pregnancy after two previous successive abortions, because two out of three will go to viability without any treatment whatsoever. This view is substantiated by the data in Table 1. After four or more spontaneous abortions, the spontaneous cure rate is very low. Therefore, the results of all therapy in habitual abortion should be cautiously appraised because of this statistically significant cure rate. In women who have lost one previous non-viable pregnancy, therapy cannot be considered as having been of value unless the cure rate with therapy is at least 80 per cent plus. After two previous abortions, the cure rate with therapy would have to be greater than 65 per cent to indicate any benefit from treatment. In short, if it can be demonstrated that hormone or other therapy has raised the cure rate significantly above the calculated spontaneous cure rate, then such a therapeutic regimen must have distinct merit and should be recommended. With a very critical attitude applied toward the various routines which have been recommended in the treatment of habitual abortion, data on almost every series thus far reported will show no improvement over the expectancy for spontaneous cure.

PATHOGENESIS

A great deal has been written on the pathogenesis of abortion.[27] Many etiological factors, including some that are little understood, have been described. Meeker[18] has presented one correlation in outline form. Although random and recurrent causes are not specifically separated, his summary can be recommended.

PATHOGENESIS OF ABORTION (Meeker)[18]

1. *Death of the Ovum:*
   - a. Hereditary Faults:
     1. Lethal and sublethal factors in the germ plasm
     2. Low vitality due to infertility of parents
   - b. Environmental Faults:
     1. Malnutrition from defective implantation
     2. Acute and chronic maternal disease
2. *Separation of the Ovum:*
   - a. Abnormalities of the decidua:
     1. Insufficient endocrine stimulus
     2. Insufficient endometrial response
3. *Expulsive Uterine Contractions:*
   - a. Factors inciting contractions:
     1. Mechanical hindrances to enlargement of the uterus
     2. Excessive violence
   - b. Excessive uterine irritability.

A somewhat different approach to the problem is that formulated by Hertig[9] in his evaluation of the causes of abortion based upon a study of lesions of the zygote as well as various maternal factors.

PATHOGENESIS OF ABORTION (Hertig)[9]

	Per Cent
Ovular Factors:	
Hydatidiform degeneration, various degrees	33.0
Abnormalities of the placenta, other	9.6
Abnormalities of the embryo, chiefly neurogenic	3.2
Maternal Factors:	
Uterine abnormalities	6.4
Low implantation of the placenta	5.6
Febrile or inflammatory maternal disease	2.0
Miscellaneous	1.2
Undetermined	38.0

These stated abnormalities are the most easily recognized. However, it is suggested that if the entire delineation were known, degeneration of the ovum itself would not only loom large but would perhaps be even more important than chorionic lesions.[28]

So far as recurrent factors in habitual abortion are concerned, the most likely causes would include persistent, chronic or uncorrected faults of the germ plasm (ova *and* sperm); abnormalities of the female reproductive tract; maternal chronic infections and metabolic diseases; female dietary and endocrine deficiencies.

In general, it would seem that although the number of abortions due to maternal factors (both random and recurrent) is small, these causes are very important. The correction of such abnormalities can be expected to be most fruitful in the salvage of subsequent pregnancies. So far as ovular factors are concerned, there is little that can be done at present because of the complexity of the problem.

A great deal is heard about the value of hormone therapy in habitual abortion. However, upon close analysis, it becomes apparent that there has been much loose talk and wishful thinking. At the present stage of knowledge, hormones can be expected to give only limited aid. Hormone supplements may improve environmental faults by improving the circulation of the uterus, ovary or endometrium.[2] They might be expected to offer additional endocrine stimulus to a lagging endometrium or ovary.[5] In addition, it seems possible that the steroid hormones may reduce excessive uterine contractility where a threatened abortion is in progress.[20]

Embryologists have for years insisted that the majority of abortions occur because of a defective ovum or placenta.[9, 15, 27] If this be the case in humans, then the hormones will be largely ineffectual. In the case of hydatidiform mole, for example, it is inconceivable that any quantity of stilbestrol could alter or improve the hydropic degeneration of the villi. When the situation has progressed to this point —and many embryos are thus blighted even in the first few weeks after nidation—it would seem that, "All the King's horses and all the King's men can't put Humpty Dumpty together again."

THE ROLE OF HORMONES IN ABORTION

A brief review of the role of hormones in abortion may aid in evaluation of what these endocrine products may be expected to accomplish in a positive or negative direction.

The Gonadotropins.

The anterior hypophysis produces pituitary gonadotropins which stimulate the corpus luteum to produce progesterone and estrogen. Potent pituitary gonadotropins are neither well evaluated nor available at this time for therapy in habitual abortion.

The chorioplacental system takes over the major production of progesterone and estrogen after the second month of pregnancy, and certain abortions occur during this critical transition period. The chorionic ectoderm produces chorionic gonadotropin as well. It is thought that the extended function of the corpus luteum in the event of pregnancy is due to the stimulus of chorionic gonadotropin. The chorionic gonadotropin differs, however, from pituitary gonadotropin and although the pituitary hormone may stimulate the formation of progesterone-estrogen, the chorionic hormone will not do so to any extent. Moreover, chorionic gonadotropin is rarely low save in a grossly deficient pregnancy. Even if it were of value in the treatment of abortion, therapeutic administration of this substance would probably require enormous quantities.[26]

The Natural Estrogens and Progesterone.

Natural estrogen is thought to prime the uterus for the inhibiting action of progesterone. In addition, progesterone prevents the excessive destruction of estrogen and is thought to aid in the conversion-degradation of estrone to estriol.[4] A balance between estrogen and progesterone is required for the delicate adjustment necessary for uterine quiescence.[23]

Prior to labor or abortion, a lowering or sudden fall in pregnandiol and/or estrogen occurs.[2, 3, 5] The administration of progesterone to bolster this progesterone deficiency has been advocated.[21] However, the administration of progesterone alone does not elevate the content of estrogen in the blood. Moreover, it is suspected that large doses of progesterone may actually operate to reduce endogenous progesterone.[7]

The Synthetic Estrogens.

It is claimed that small amounts of stilbestrol cause increased secretion of progesterone and natural estrogen, probably by the placental syncytium.[21] This is apparently the result of increased utilization or excretion of chorionic gonadotropin. Stilbestrol is used in the treatment of abortion, not as an estrogen but as a stimulant to the production of progesterone and natural estrogen.[21]

Thyroid Hormones.

Low thyroid function is known to result in pituitary failure and also in ovarian deficiency. Although the cause and effect are difficult to demonstrate in abortion, subclinical hypothyroidism is more common than is appreciated and administration of thyroid extract is therefore often valuable.[5, 19]

It is likely that the alert obstetrician can modify certain factors in either isolated or habitual abortion. These factors would be, in the great majority of cases, maternal faults. If, as Hertig[9] has noted, these constitute only 15 per cent of the observed factors operative in abortion, therapeutic successes will be very limited.

TREATMENT

Despite these conclusions, physicians should not become too pessimistic, for there is logic in certain routines and medications which have been of value over the years. The author believes in treating the patient who is a sequential or habitual aborter. The medical management of such patients should include three plans: (1) preconceptual treatment, if possible; (2) postconceptual treatment; and, (3) emergency treatment.[21] Therapy may be either liberal or conservative according to the views of the individual physician. However, eagerness, gullibility, a "give-it-anyhow-for-psychic-effect" attitude, as well as a reluctance to abandon one therapeutic weapon when another takes its place, have led to promiscuous and irrational hormone therapy.[10]

Prophylactic therapy is of obvious value. The patient and her husband should be investigated and treated preconceptually whenever possible.[6, 10, 25] Fundamentally, general hygiene and other methods calculated to put both husband and wife in the best physical and mental state are indicated. The basal metabolic rate should always be determined, for thyroid therapy may be of great value even where minor degrees of hypothyroidism exist. Cervicitis and other infections should be eradicated, pelvic tumors should be eliminated, and retroversion of the uterus may require correction—before the next pregnancy. A complete semen evaluation, as is done in sterility study, is valuable, and suitable treatment should be administered if the specimen is consistently deficient. Supportive or supplementary hormone therapy may be initiated very early in pregnancy, when, for example, the basal body temperature chart or Friedman test confirms the presence of pregnancy. Limitation of activity, avoidance of douches and intercourse are advised. If abortion threatens, bed rest, mild sedation, suspension of coitus, and avoidance of purges or excitement are helpful. At least one authority insists that such a regimen is of as much value in therapy as are the much-discussed hormones.[10]

Regarding a specific program of therapy, it is possible to outline the medications and routines thus:

1. Agents and methods which have a rationale and are of distinct value when indicated in prophylactic therapy of habitual abortion. They may include:
   a. Reduction of pathological factors in husband and wife.
   b. All essential vitamins in optimum amounts, preferably in the diet.
   c. A high protein diet.
2. Agents which have possible rationale in habitual abortion:
   a. Stilbestrol or estrogen-progesterone therapy.
   b. Progesterone or estrogen alone.
3. Agents for which there is evidence suggestive of value in habitual abortion:
   a. Vitamin C, E (?), K.
   b. Mixed gonadotropins.

The author does not believe that vitamin E can be recommended as a routine therapeutic agent in the treatment of habitual abortion. According to the Council on Therapy of the American Medical Association, (1) there is lack of convincing evidence of its value in habitual or other abortion, and (2) variation of dosage is wide in patients reportedly benefited by the preparation.[9]

During recent years, two significant hormone regimens have been advanced in the intercurrent treatment of habitual abortion. One is the stilbestrol regimen as outlined by Smith and Smith.[24] This program has been evaluated in a small but carefully selected series of cases. Rather convincing evidence for its successful use in repeated abortion has been presented. This routine is as follows:

Stilbestrol, 5.0 mg. daily, is started in the sixth or seventh week of pregnancy. The daily dose is increased 5.0 mg. every two weeks. After 16th week it is increased by a daily dose of 5.0 mg. per week. Stilbestrol is discontinued at 35th week of pregnancy.

Unfortunately, the cost of stilbestrol to a private patient for the course recommended is about 45 dollars at this time.

Vaux and Rakoff[29] have suggested a combination of progesterone and natural estrogen in the therapy of habitual abortion. A statistical appraisal of their results reveals a significant increase in the fetal salvage following the use of this medication. The suggested regimen follows:

Progesterone, 10 mg., and alpha-estradiol benzoate, 1.66 mg., given together intramuscularly every two or three days. This treatment is begun as early in pregnancy as possible and is carried to the period of viability or later.

This treatment also is expensive and entails the hypodermic administration of the required medication.

An emergency routine for threatened abortion, as outlined by Karnaky,[14] also has advocates:

Initial dose of 100-250 mg. of stilbestrol intramuscularly (25 mg. into the cervix). Then, 25 mg. orally, every 15 minutes until bleeding and/or pain cease. Daily doses thereafter of 10-100 mg., tapering off if no bleeding or pain recurs. Daily dose is increased sharply if bleeding or pain recurs.

Certain patients may be expected to retain the fetus and carry it successfully with this regimen, particularly where uterine hyperirritability is apparent. However, vaginal smear studies of patients presenting signs and symptoms of an accident of early pregnancy indicate that with the onset of uterine bleeding, the pregnancy often has actually terminated although the products of conception may still be retained.[1] Nevertheless, in an effort to do everything possible to salvage a threatened pregnancy, the use of such a routine is justified.

REFERENCES

1. Benson, R. C., Traut, H. F.: The vaginal smear as a diagnostic and prognostic aid in abortion, J. Clin. Endocrinol. (In Press.)

2. Browne, J. S. L., Henry, J. S., Venning, E. H.: Significance of endocrine assays in threatened and habitual abortion, Am. J. Obstet. and Gynec., 38:927, Dec. 1939.

3. Cohen, S. L., Marrian, G. F., Watson, M. C.: Excretion of estrin during pregnancy, Lancet, 1:675, March 1935.

4. Corner, G. W.: Glandular Physiology and Therapy, A.M.A., Chicago, 1942.

5. Delf, E., Jones, G. L. S.: Normal and Pathological Physiology in Pregnancy, Williams and Wilkins, Baltimore, 1948.

6. Eastman, N. J.: Editorial comment on habitual abortion, Obstet. and Gynec. Survey, 2:17, Feb. 1947.

7. Hamblen, E. C.: Endocrinology of Women, Springfield, Ill., Chas. Thomas, 1945.

8. Hamblen, E. C.: Some clinical observations on endocrinology of abortion, Am. J. Obstet. and Gynec., 41:664, April 1941.

9. Hertig, A., Livingstone, R. G.: Medical progress; spontaneous, threatened and habitual abortion; their prognosis and treatment, New England J. Med., 230:797, June 1944.

10. Hoffman, J. M.: Symposium on recent advances in gynecology and obstetrics; uses and abuses of endocrine therapy, M. Clin. North America, 29:1396, Nov. 1945.

11. Hunt, A. B.: Habitual abortion, M. Clin. North America, 30:965, July 1946.

12. Javert, C. T., Stander, H. J.: Plasma vitamin C and prothrombin concentration in pregnancy and in threatened,

spontaneous and habitual abortion, Surg. Gynec. and Obstet., 76:115, Jan. 1943.

13. Javert, C. T., Finn, W. F., Stander, H. J.: Primary and secondary spontaneous habitual abortion, Am. J. Obstet. and Gynec., 57:878, May 1949.

14. Karnaky, K. J.: Use of stilbestrol for treatment of threatened and habitual abortion and premature labor; preliminary report, South. M. J., 35:838, Sept. 1942.

15. Mall, F. P.: On the frequency of localized anomalies in human embryos and infants at birth, Am. J. Anat., 22:838, July 1917.

16. Malpas, P.: A study of abortion sequences, J. Obstet. and Gynec. Brit. Emp., 45:932, Dec. 1938.

17. Malpas, P.: Categories of abortion and abortion-stillbirth sequences, J. Obstet. and Gynec. Brit. Emp., 49:65, Feb. 1942.

18. Meeker, S. R.: Working classification of causes of abortion, J.A.M.A., 123:680, Nov. 1943.

19. Pratt, J. P.: Ovarian therapy, Endocrinology, 16:45, Jan.-Feb. 1932.

20. Reynolds, S. R. M.: Physiology of the Uterus, Paul B. Hoeber, New York, 1939.

21. Rutherford, R. N.: Spontaneous and induced abortion; modern concepts of their significance, pathogenesis, diagnosis and treatment, West. J. Surg., 51:257, July 1943.

22. Sachs, E.: Therapeutic Problems of Today, Teva. Tit., Jerusalem, 1948.

23. Smith, O. W., Smith, G. V., Schiller, S.: Estrogen and progestin metabolism in pregnancy; spontaneous and induced labor, J. Clin. Endocrinol., 1:461, June 1941.

24. Smith, O. W., Smith, G. V., Hurwitz, D.: Increased excretion of pregnandiol in pregnancy from diethylstilbestrol with special reference to prevention of late pregnancy accidents, Am. J. Obstet. and Gynec., 51:411, March 1946.

25. Siegler, S. L.: Fertility in Women, J. B. Lippincott, Phila., 1945.

26. Stander, H. J.: Textbook of Obstetrics, D. Appleton-Century, New York, 1945.

27. Taussig, F. J.: Abortion, Spontaneous and Induced, C. V. Mosby, St. Louis, 1936.

28. Traut, H. F.: Personal communication.

29. Vaux, N. V., Rakoff, A. E.: Estrogen-progesterone therapy; new approach in treatment of habitual abortion; studies indicating its rationale in 24 treated cases, Am. J. Obstet. and Gynec., 50:353, Oct. 1945.

Skeletal Suspension in the Treatment of Decubiti

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SUMMARY

In the usual sacral decubitus, pressure may be relieved by skeletal suspension from Kirschner wires placed in the ilian crests. Pressure sores over the scapulae and thoracic spine may be handled by placing Kirschner wires through the clavicles. Both of these methods lend themselves to the preoperative care of a patient being prepared for the plastic closure of a decubitus.

IN the handling of large numbers of war casualties, one troublesome problem was the large number of decubiti encountered. Primarily, these were found in patients with injury to the spinal cord, but they occurred also in patients with other severe injuries such as burns and abdominal and chest wounds. The decubiti encountered were not only large but multiple, involving in the same patient, the sacral and scapular areas, the anterior surfaces of both knees, both shins, both heels, both trochanteric and both iliac areas. Decubiti are, of course, much less frequently encountered in civilian practice, but they do occur in patients with severe burns, in paraplegics and in patients debilitated from any cause.

Extensive decubiti almost always produce toxemia and usually pronounced anemia along with a low leukocyte count and low hematocrit reading. Recently it has been shown that pronounced hypoproteinemia occurs as well. Mulholland,[4] who carefully checked the protein intake and output in some 35 patients, found that there was a negative nitrogen balance with a consistently low blood protein value in all of them. He found that intubation and forced feeding with a high protein diet were of more value than blood transfusions. In patients with severe burns and in debilitated patients of all types the hypoproteinemia precedes and is a direct cause of the ulcer. In paraplegics the hypoproteinemia is secondary to the exudation of protein from the decubitus.

Obviously, it is best to prevent decubiti if possible, first by the maintenance of adequate nutrition, and secondly by the avoidance of prolonged pressure. Once ulcers have formed they are difficult to control. Aside from any other consideration, decubitus ulcers increase tremendously the nursing care required for these patients.

Plastic closure of such ulcers has been recommended by many investigators[1, 2, 7] since the termination of World War II. Ulcers which have attained a large size, however, are usually infected and necrotic. Furthermore, the underlying viable tissue may be so ischemic that a plastic closure or the application of a skin graft is out of the question. No method of treatment of these lesions is satisfactory unless pressure is removed from the area.

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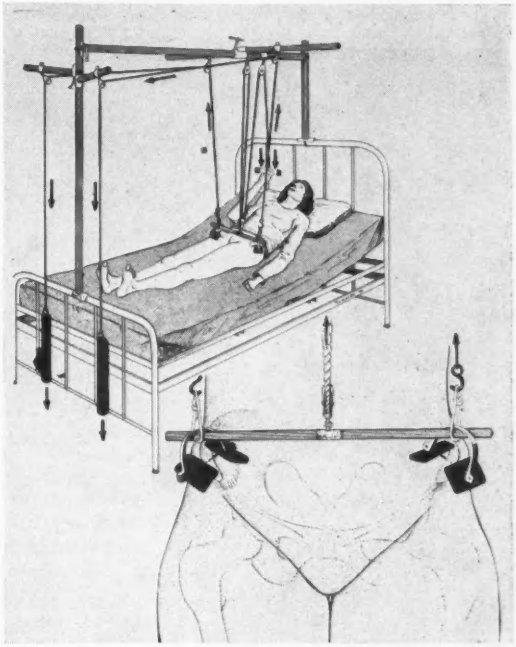

Figure 1.—Skeletal suspension through the iliac crests.

The usual methods of avoiding pressure by the use of air rings, air mattresses and routine turning of the patients are fairly satisfactory for the treatment of smaller decubiti, but are inadequate for the control of extensive ulcers. A procedure which more effectively reduces pressure on the affected areas is the use of overhead suspension by means of Kirschner wires placed through the iliac crests. This method was described by Westhues[6] and by Klapp[3] in the German war literature, and experience with it was reported by Schneider and Stapff.[5] The author has used the method, with modifications.

METHOD

With local anesthesia (in paraplegic patients anesthesia is unnecessary) Kirschner wires are drilled through the most anterior portions of both iliac crests, the wires being placed as deep in the ilium as the configuration of the patient's body will allow. To avoid slipping of the wire and consequent pressure, heavy felt should be placed between the inner sides of the bows and the patient's skin. (Figure 1 shows the procedure in detail.) The wire

spreader bows are hooked onto a spreader bar and traction is applied by means of weight. Depending upon the weight of the patient, the weight on each bow varies from 20 to 25 pounds, but the traction should not be heavy enough to lift the patient from the bed. A rope attached to the middle of the spreader bar has a handle on the other end which enables the patient to raise himself whenever it is necessary to use a bedpan or change the dressings. All traction is released several times a day and the patient is turned on either side for periods of one hour each. This method has been used even in the presence of rather moist dressings around a suprapubic drainage tube.

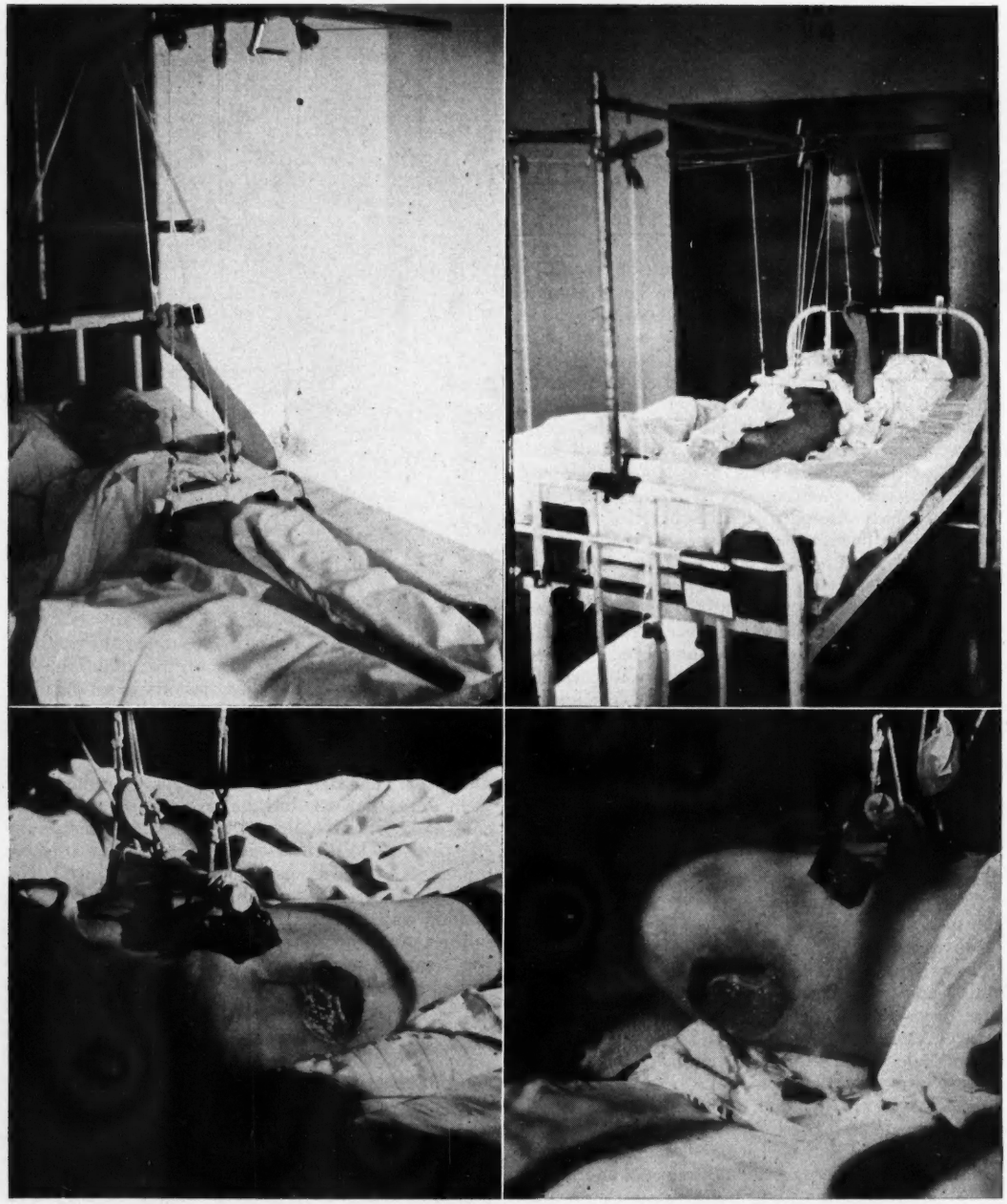

Figure 3.—Photographs of a patient with multiple decubiti who has iliac suspension. Upper pictures show the overall arrangement of the skeletal suspension set-up. The lower pictures show a Kirschner wire placed through the iliac crests with the felt pads protecting the skin from the wire bows. Bilateral trochanteric decubiti are also shown.

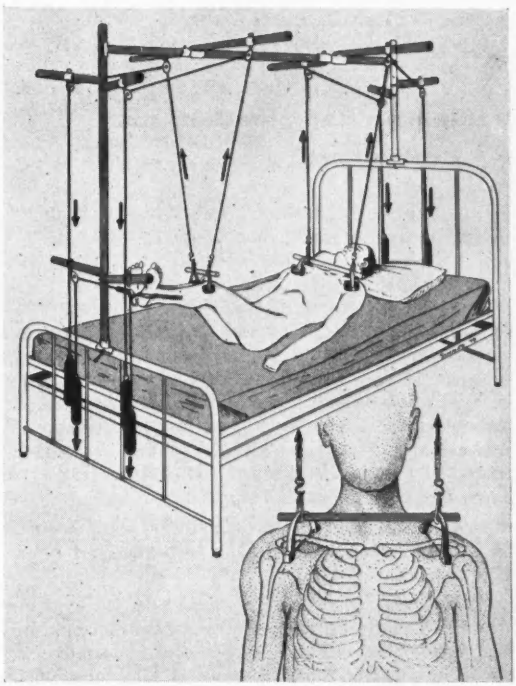

Figure 2.—Skeletal suspension through the clavicle and through the tibial tuberosities.

Pressure sores over the scapulae and thoracic spine may require some shoulder girdle suspension. Obviously, not much weight can be used. A method of suspension by Kirschner wires through the clavicles is diagrammed in Figure 2. As the patients are all considerably underweight, no difficulty is encountered in placing a wire through the midportion of the clavicle. Again it is advisable to pad the inner sides of the bows to avoid slipping of the wires with consequent pressure sores. The author has put only five to ten pounds weight on each of these wires lest more traction dislocate the clavicles.

By means of this overhead suspension even extensive, infected decubiti have been brought under control. With avoidance of pressure further spread and extension of decubiti is prevented, and after several weeks of this balanced suspension the blood supply to the ulcerated area improves. Necrotic skin and underlying tissue are excised and the bed of the ulcer is ready for skin grafting or plastic closure. Skin grafts applied to these ulcers have taken whenever pressure on the grafted area could be prevented.

The method described has been employed principally in patients with injury to the spinal cord. It is suitable for the treatment of bedsores resulting from other causes, with the following exceptions:

1. In civilian practice occasionally a patient is encountered who has been bedridden for years with the eventual production of sacral decubiti. Osteoporosis is always present in such patients and the iliac bone is not strong enough to sustain a Kirschner wire. It has been suggested by Klapp[3] that, for heavy patients, additional overhead support can be obtained by means of transfixion of the symphysis and both pubic bones with a Kirschner wire. The author has had no experience with this method, but it might be of value in patients with osteoporosis.

2. In patients with burns or wounds involving the iliac crests or with nearby draining colostomies, it is of course inadvisable to use iliac suspension. In one such case, as shown in Figure 3, Kirschner wires were placed through both tibial tubercles and some of the pelvic weight supported in this manner. The weights used should allow the patient's back to rest lightly on the bed so that a hand may be slipped between the patient's back and the bed without difficulty. The adhesive skin traction on the lower legs is used merely to support the lower legs. Right angle suspension of the legs such as that used in the treatment of fractured femurs in infants is impractical because of the poor circulation in these patients.

Balanced body suspension by means of Kirschner wires placed through the iliac crests is useful in the care of patients with large decubiti. Shoulder girdle suspension to prevent pressure on the scapulae can be obtained by placing Kirschner wires through the clavicles.

REFERENCES

1. Freeman, B.: The treatment of bedsores in paraplegic patients, Surgery, 21:668-674, Mar. 1947.

2. Gibbon, J. H., and Freeman, L. W.: The primary closure of decubitus ulcers, Ann. Surg., 124:1048-1164, Dec. 1946.

3. Klapp, W.: A note upon R. Klapp's method of pelvic suspension, Zeit F. Chirurg., 69:1567-9; Abs. Bull. of War. Med., 3-493, 1942-43.

4. Mulholland, J. H., et al.: Protein metabolism and bedsores, Ann. Surg., 118:1015-1023, Dec. 1943.

5. Schneider, J., and Stapff, R.: Experience with Klapp's method of wire suspension, applied to the pelvis, Zeit F. Chirurg., 69:1559-66.

6. Westhues, H.: Half suspension of the pelvis, Der. Chirurg., 14:489-93, Aug. 15, 1942; Abs. Bull. War. Med., 3:440, 1942-43.

7. White, J. C., and Hamm, W. F.: Primary closure of bedsores by plastic surgery, Ann. Surg., 124:1146-47, Dec. 1946.

Detection of Pulmonary Tuberculosis

Comparative Value of Routine Radiologic Examinations and Routine Laboratory Procedures

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SUMMARY

The abnormalities disclosed by the usual laboratory diagnostic procedures (blood cell count and hemoglobin determination, sedimentation rate determination, urinalysis, and serologic test for syphilis) are compared with the number revealed by stereophotoroentgen chest examination in a series of 951 patients.

The number of significant abnormalities uncovered by the routine stereophotoroentgen examination of the chest was comparable to the number disclosed by the usual laboratory procedures used in patient evaluation.

Some form of radiologic examination of the chest should be included in the routine laboratory procedures required for patient evaluation.

THE value of some form of radiologic chest examination in the detection of unsuspected pulmonary tuberculosis has been proved by numerous surveys. The value of such a procedure as a routine part of the complete patient evaluation, however, has not been generally recognized or admitted. Certain laboratory studies, namely, urinalysis, blood cell count, sedimentation rate determination, and serologic examination for syphilis, are considered essential parts of such a case study, and omission of them would be cause for criticism in most clinics and hospitals. Unless there are specific complaints referable to the respiratory system, however, radiologic chest examination may not be made. The study to be reported here was undertaken for two reasons: (1) to compare the number of significant abnormal findings disclosed by the usual laboratory procedures and by roentgen examination of the chest, in the same series of patients, and (2) to demonstrate, on the basis of the comparative amount of pulmonary disease thus uncovered, the value of including some form of radiologic examination of the chest among the routinely required laboratory procedures for patient evaluation.

It has been reported that routine blood cell counts reveal blood dyscrasias in a small fraction of one per cent of patients.[10]

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Joslin[6] estimated that routine analysis of urine uncovered diabetes in 0.4 per cent of patients examined. Wilkerson and Krall[11] reported a survey of 3,500 citizens of Oxford, Massachusetts, in which 40 cases of diabetes known to physicians, and 30 additional unknown cases, were found. It is estimated that there are at least 1,000,000 undiagnosed cases of diabetes in this country.

Routine serologic tests for syphilis were positive in 2.4 per cent of white males examined for Selective Service.[9]

Tuberculosis revealed by mass chest radiography in United States Selective Service examinations was the cause of rejection in 1.4 per cent of examinees.[3] Graham[2] reported that in a series of 2,067 obstetrical patients observed in private practice, routine roentgenologic chest examinations revealed active tuberculosis in 0.77 per cent and significant parenchymal disease in 3.44 per cent. Block and his associates[1] found significant abnormalities by fluoroscopic examination in 21.3 per cent of 15,000 University of Chicago students. They concluded that in the 15 years prior to the introduction of routine x-ray examination, 3,000 patients with clinically important pulmonary tuberculosis passed through the outpatient department without detection of the disease. They estimated that throughout the country 600,000 tuberculous perons undergo medical examinations each year without detection of this condition. Hodges[5] at the University of Michigan Hospital found, by photofluorographic chest examination of 7,841 patients, deviations from normal in 14.1 per cent and abnormalities demanding more extensive x-ray examination in 9.3 per cent.

In a study of 153 patients with carcinoma of the lung Overholt[7] discovered that in 60 per cent not only had an incorrect diagnosis been made, but treatment based on that diagnosis had been maintained for long periods of time. In the series he reported, the length of time elapsing between the onset of symptoms and consultation with a physician averaged three months. Three months more elapsed before the physician requested chest x-ray studies, and the correct diagnosis was not made until another six months had passed. Thus definitive treatment was delayed for an average of nine months from the time of the first consultation. Early chest roentgenograms with necessary additional study would have obviated many months of delay.

The figures cited are the results of independent surveys in different groups of individuals. In the study here reported the results of five laboratory procedures, all applied to each patient, are compared.

For this purpose, the records of 951 patients, treated on a private practice basis, who consulted the diagnostic section of this Clinic from August through December, 1947, were taken at random. No records of hospitalized patients were included. There were 336 males and 615 females in the series. The ages ranged from 12 to 82 years with an average of 42.9 years for males and 40.5 years for females. In all of these cases, a full history was taken, a complete physical examination made, and laboratory procedures consisting of a complete blood cell count, hemoglobin and sedimentation rate determinations, urinalysis, serologic examination for syphilis, and stereophoto roentgen examination of the chest were carried out. Other investigative procedures depended upon indications in the individual case. It should be emphasized that many patients with specific chest complaints were not included in the group, since such patients were sent directly to the department of diseases of the chest for study. Neither were any obstetric patients included. With these two exceptions, the series represents a cross-section of adult patients observed in private practice.

PHOTOROENTGEN CHEST STUDIES

The merits of various screening methods for chest disease will not be discussed here. Hilleboe and Morgan[4] have covered this subject well. This clinic uses the photoroentgen method which utilizes the 4x5 inch stereo film, the advantages of which have been summarized by Potter, Douglas, and Birkelo.[8] It is the opinion at this clinic that photoroentgenograms made by this method, when interpreted by a competent roentgenologist, constitute a dependable screening method for existing chest disease. The inconvenience to the patient is slight and no more time-consuming than the drawing of a blood sample.

Analysis is based on results of chest photoroentgenograms in 951 cases. Normal findings were reported in 758 cases (79.7); some form of definite abnormality was found in 148 cases (15.6 per cent); and equivocal or indefinite findings in 45 cases (4.7 per cent). (See Table 1.) The percentage of cases in which definite abnormalities were found is slightly lower than that reported for screening methods by other observers. There are three possible explanations for this difference: (1) although further roentgenographic investigation in the 45 cases in which indefinite or equivocal findings were reported revealed significant abnormalities in a high percentage of them, these were not included in the total figure; (2) few patients with specific chest complaints were included in the study; and (3) minor deviations from normal (minute calcifications) were considered insufficient to warrant a report of abnormality.

TABLE 1.—*Results of Stereophotoroentgen Chest Examinations*

	No.	Per Cent
Patients examined	951	
Patients with abnormalities	148	15.6
Patients requiring additional roentgenographic study	45	4.7
Patients with negative findings	758	79.7

TABLE 2.—*Abnormalities Revealed by Stereophotoroentgen Examination in 951 Cases*

		No.	Per Cent
Lung lesions		77	8.1
Minimal tuberculous lesions	7		
Hilar and parenchymal calcification and/or scarring	55		
Pulmonary fibrosis	6		
Increased markings	4		
Emphysema	4		
Thoracoplasty for tuberculosis	1		
Pleural lesions		10	1.1
Calcified pleura and/or old scarring	7		
Pleural effusion	3		
Cardiovascular lesions		44	4.7
Enlarged heart	34		
Enlarged aorta	9		
Aortic aneurysm	1		
Skeletal lesions		7	0.7
Scoliosis	3		
Fractured ribs	2		
Tuberculosis of spine	1		
Osteomyelitis of rib	1		
Tumors		2	0.2
Dermoid cyst	1		
Enlarged nodes	1		
Miscellaneous		8	0.8
Cervical rib	2		
Thyroid enlargement	4		
Substernal thyroid	1		
Calcified cervical nodes	1		
Abnormal photoroentgenograms		148	15.6
Additional roentgenography requested		45	4.7
Negative photoroentgenograms		758	79.7

A summary of abnormalities found is given in Table 2. Significant pulmonary disease was found in 21 cases (minimal active tuberculosis in seven, pulmonary fibrosis in six, emphysema in four and abnormally increased markings in four). Definite evidence of parenchymal disease characterized by hilar or massive calcifications throughout both lung fields was noted in 55 cases. The incidence of minimal tuberculosis (seven cases) is significant and should be emphasized.

SEROLOGIC EXAMINATIONS FOR SYPHILIS

The reaction to the standard Kahn test for syphilis was positive in eight (0.84 per cent) of the 951 patients examined and results of Kolmer-Wassermann tests were positive in six cases (Table 3). In these eight cases, a diagnosis of syphilis was made and treatment instituted.

SEDIMENTATION RATE DETERMINATIONS

The Westergren method of determining the sedimentation rate was used in this study. The normal value for males is usually considered to be from 0 to 15 mm. and for females from 1 to 20 mm. in one hour. Many of the workers at this clinic feel that these accepted normal values are too low; they consider a significant rate to be over 20 mm. in one

TABLE 3.—*Results of Serologic Tests for Syphilis*

	No.	Per Cent
Total number of cases	951	
Positive reactions	8	0.8
Negative reactions	943	99.2

hour for males and over 30 mm. for females. On the basis of the latter values, there were 159 patients (16.8 per cent) with higher than normal rates (Table 4). Of these, 58 were males and 101 females. It should be pointed out that these reported levels of sedimentation activity were not corrected for anemia and that slight anemia was frequently present.

TABLE 4.—*Results of Sedimentation Rate (Westergren) Determinations**

	Male	Female	Total	Per Cent
Total number of cases	336	615	951	
Abnormal rates	58	101	159	16.8
Normal rates	278	514	792	83.2

*Normal range: Males 0-20 mm., females 0-30 mm. in one hour.

HEMOGLOBIN DETERMINATIONS

Blood-analysis in all cases in this series included determination of hemoglobin concentration, and counts of erythrocytes, leukocytes and differential leukocytes, but only the hemoglobin concentration values have been tabulated. Inasmuch as most deviations from normal in the blood analysis occurred in the hemoglobin value, it is considered satisfactory for this comparative study. On the basis that 15 gm. of hemoglobin per 100 cc. of blood equals 100 per cent, the hemoglobin concentration values were below 75 per cent (11.5 gm. per 100 cc.) in 70 cases (7.4 per cent) (see Table 5). In four cases the patients were males; in 66, females. No cases of leukemia or other blood dyscrasias were observed in this series.

TABLE 5.—*Results of Hemoglobin Determinations**

	Male	Female	Total	Per Cent
Total number of cases	336	615	951	
Abnormal results	4	66	70	7.4
Normal results	332	549	881	92.6

*Normal: 11.5 gm. per 100 cc. (75%) to 15 gm. per 100 cc. (100%).

URINALYSES

There were significant deviations from normal in the urine of 124 patients (13.1 per cent) (Table 6). Sugar appeared by the Benedict's reducing test in five cases, and in all of these cases further studies revealed the presence of diabetes mellitus.

DISCUSSION

A numerical summary of the abnormalities disclosed by the usual laboratory procedures and by the routine stereophotoroentgen chest examination in the series of 951 patients is given in Table 7. These findings are evidence of the importance of

TABLE 6.—*Results of Urinalyses*

	No.	Per Cent	No.	Per Cent
Total number of cases			951	
Abnormal results			124	13.1
Leukocytes	54	5.7		
Erythrocytes	8	0.9		
Albumin	57	6.0		
Sugar	5	0.5		
Normal results			827	

these laboratory procedures in the evaluation of the patient's condition either as screening procedures or as specific tests. The fact that most patients referred directly to the department of diseases of the chest were excluded from this study gives added significance to the results of stereophotoroentgen examination of the chest in routine practice.

TABLE 7.—*Summary of Results of Routine Laboratory Procedures in 951 Cases*

Procedures	Number of Cases in Which Abnormalities Were Present			
	No.	Per Cent	No.	Per Cent
Photoroentgen chest examinations			148	15.6
Significant pulmonary disease	21	2.2		
Minimal active tuberculosis	7	0.7		
Cases in which additional roentgenographic chest study was required	45	4.7		
Serologic test for syphilis			8	0.8
Sedimentation rate (Westergren) determination			159	16.8
Hemoglobin determination			70	7.4
Urinalysis			124	13.1
Sugar reduction for diabetes	5	0.5		

The number of patients in whom clinically significant abnormalities were demonstrated as a result of the photoroentgen chest examination, was comparable to or greater than the number of patients in whom significant abnormalities were demonstrated by laboratory screening procedures usually considered essential — hemoglobin and blood sedimentation rate determinations, and urinalysis. The number of cases of clinically important pulmonary tuberculosis uncovered as a result of further study of chest abnormalities was comparable to the number in which disease was revealed by the more specific serologic examination of the blood for syphilis and to the number in which diabetes mellitus was disclosed by further studies in cases in which sugar was found in the urine.

It is the authors' opinion, as a result of this survey, that some form of radiologic examination of the chest is as important in the evaluation of a patient as are the laboratory procedures which are usually considered essential in such an evaluation.

REFERENCES

1. Block, R. G., and Tucker, W. B.: Indispensability of routine x-ray examinations of chest in general clinic, Am. Rev. Tuberc., 50:405-417, Nov. 1944.

2. Graham, H. K.: Routine chest roentgenograms in pregnancy; a supplementary study, West. J. Surg., 55:438-441, Aug. 1947.

3. Greve, C. H., Clark, M. L., McGill, K. H.: Physical examinations of Selective Service registrants, January 1944-August 1945, Medical Statistics Bulletin No. 4, National Headquarters, Selective Service System, Washington, D. C., June 1, 1946, p. 12.

4. Hilleboe, H. S., and Morgan, R. H.: Mass Radiography of the Chest, Year Book, Chicago, 1945, pp. 22-42; 98-125.

5. Hodges, F. J.: Fluoroscopic examination of the chest, Radiology, 38:453-461, April 1942.

6. Joslin, E. P., Root, H. F., White, P., and Marble, A.: The Treatment of Diabetes Mellitus, Lea & Febiger, New York, 7th ed., 1940, p. 38.

7. Overholt, R. H.: A common masquerading lung disease, New York State J. Med., 42:1657-1662, Sept. 1, 1942.

8. Potter, H. E., Douglas, B. H., Birkelo, C. C.: The miniature x-ray chest film, Radiology, 34:283-291, March 1940.

9. Results of serological blood tests for syphilis on Selective Service registrants, U. S. Public Health Service, Federal Security Agency, Oct. 1942.

10. Wilson, N. J.: Early diagnosis of disease of the chest, New England J. Med., 232:301-309, March 15, 1945.

11. Wilkerson, H. L. C., and Krall, L. P.: Diabetes in a New England town, J.A.M.A., 135:209-216, Sept. 27, 1947.

A Simple Infant Transfusion Kit for Occasional Use

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MANY occasions on which a small transfusion would benefit a sick or convalescent infant are passed up because of the technical difficulties involved. Usually the major stumbling block is lack of equipment, particularly sterile tubing. Few physicians care to assemble, autoclave and put aside equipment that is used so seldom.

However, a satisfactory infant transfusion set can be assembled on short notice from materials already available in most offices. Required are:

One 50 cc. syringe with adapter.
One 10 cc. Luer-Lok® syringe.
One three-way stopcock (from lumbar puncture set).
One set disposable plastic intravenous tubing (Baxter or Abbott).

The plastic tubing is packed in sterile condition, has a needle adapter on one end, and costs little. After the syringe and three-way stopcock are boiled, a length of the plastic tubing (15 to 20 inches) is cut with sterile scissors and attached to the small arm of the three-way stopcock where it is firmly tied with heavy thread. The needle adapter and any other slip joints in the tubing are also tied. The assembly is completed by attaching the two syringes to the proper arms of the three-way stopcock. The plastic tubing is discarded after it has been used.

A suggested routine for using the kit in the office follows:

The blood of the infant and of the donor is cross-matched. An 18-gauge needle is attached to the 50 cc. syringe and 8 cc. of sterile 2.5 per cent sodium citrate solution placed in the syringe. Forty-five cc. of blood is drawn rapidly from the donor so that the turbulence in the syringe produces adequate mixing of the blood and citrate without shaking.

The 10 cc. syringe, which is in place on the three-way stopcock, is used to fill the stopcock, the tubing and the needle with sterile saline solution (from a rubber capped vial) and a few cubic centimeters of the solution is left in the syringe. After the needle is inserted under the skin, gentle traction on the syringe will bring blood into view in the adapter as soon as the vein is entered. This is very helpful in dealing with small veins.

The large syringe is then attached to the three-way stopcock and blood introduced either directly or by repeatedly filling the 10 cc. syringe. The smaller syringe is the more easily controlled.

Many variations suggest themselves. If only slight pressure is needed, the large syringe can be suspended as a gravity reservoir. After the blood has been given, a saline drip can be connected to the three-way stopcock if desired.

The advantages of this arrangement are: (a) the parts are standard items of office equipment; (b) the parts can be assembled in a few minutes, and returned to their ordinary function after use; (c) the use of disposable plastic intravenous tubing is inexpensive and makes autoclaving and storage of rubber tubing unnecessary.

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Psychiatric Problems in Children

Part II

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In the article printed in the May issue of this journal, three large groups or kinds of psychiatric disorders of children were reviewed. I suppose that in certain important respects they are of least interest to a group of general practitioners. The syndromes of childhood neurosis, psychosis and aggressive behavior disorder are all of them least likely to come to your attention—or at least, less often than some others. These syndromes are really the end-products or, more precisely, very extreme forms of psychiatric disorder in childhood. They require relatively little specialized experience or training to recognize and their severity and chronicity are such as to require the time as well as the competence which the busy practitioner cannot perhaps be expected to possess and to give. Also it is probably less important that the correct, shorthand diagnostic title be applied to the disorder by the physician who is consulted about one of these severe disorders than that he direct the family to appropriate facilities prepared to make some effort for the care and treatment of the patient.

This referral for treatment is of itself a serious problem because of the great shortage of psychiatric clinics for children everywhere in this country and of insufficient trained personnel to staff such clinics as exist. The amount of time as well as trained skill (which itself takes years to acquire) which is necessary to be even of some help in these serious disorders is such that most existing clinics even with fairly large staffs are usually overburdened and struggle with long waiting lists for admission.

Nevertheless, there may have been some advantage in reviewing these gross clinical forms of disorder. The advantage consists in that they may be orientation points from which to understand the overwhelming majority of minor, less severe disturbances of children, most of which do not come very near to fitting into any of the three categories that were reviewed. I mean that a very great number of children brought not only to general practitioners but to child psychiatrists as well have symptoms—or at least their parents have complaints about them—which cannot be easily classified either as neurotic or psychopathic. Such children show mixtures of both types of difficulty—that is, symptoms of neurosis and of behavior disorder concurrently. They manifest, in other words, peculiar combinations of neurotic conflict *and* difficulty in self-restraint of their hostile aggressive or of their innate egocentric impulses. One sees, for example, quite frequently children who, in certain situations or at certain times, find it impossible to restrain their cruelty, or to be frank, honest, and to respect others' property and at other time show severe phobias, night terrors, or other somatic neurotic symptoms.

Second of two lectures in the course in psychiatry for the general practitioner, sponsored by the University of California Medical School, University Extension, presented at the Langley Porter Clinic, February 3, 1949.

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COMPLAINTS FREQUENTLY MADE BY PARENTS

Parents also complain that a child may be at once intimidated and fearful with his peers and excessively autocratic and abusive with younger children or siblings, while at the same time fidgety, restless generally, a poor sleeper and subject to frequent gastrointestinal upsets. Frequent, too, are the complaints about the difficulty in acquiring personal and social habits or discarding more infantile traits at later chronological ages. Persistent thumb-sucking, for example, with the current warnings from orthodontists that it may lead to severe malformation of the dental arches, is a frequent subject of much parental anxiety. Enuresis, diurnal as well as nocturnal, and recurrent fecal soiling, poor appetite with some malnutrition and susceptibility to minor infections, or frequent and severe temper tantrums, destructive and violent hostility to a younger sibling expressing unresolved, extreme rivalry, and a host of other such individual complaints with little or no evidence of a more total or severe neurotic disorder, may be the immediate reason for the consultation. Masturbation, excessive sexual curiosity and preoccupation often frighten parents, while repeated episodes of stealing sometimes raise visions of future criminality. Literally, the list of such individual combinations of symptoms and behavior difficulties is almost inexhaustible and I am certain it can be supplemented almost endlessly by everyone of you out of your own experience in practice. All this does not even touch upon a similar variety of difficulties and anxieties parents have with infants and young children under two or three years of age with respect to feeding, elimination, general health and primary socialization and domestication in habit training of cleanliness, self-care, and so forth.

All these congeries of symptoms and problems, all these less severe and in-between conditions, make it necessary to formulate a wider conceptual frame-

work and viewpoint than that of the traditional nosological entities we have discussed. We need, in other words, a way of looking at the otherwise bewildering variety of physiological and psychological disturbances of children which will be more useful to the medical man than the notions of individual neurosis, psychosis or behavior disorder. It is at this point that I feel I can tell the experienced general practitioner little that he does not already know and understand.

The physician established for some years in a community begins to know not only the physiological condition of the individual patient, child or adult, who may over a period of time consult him repeatedly. He begins to know his patient as a person, that is, as a unique member of a particular family and of other groups with a particular vocation and avocational interests and adjustments, with particular hobbies, preferences, aversions, with a certain intelligence and social and economic and educational background and status; in short, the physician comes to know the patient's advantages and disadvantages. The physician acquires in his repeated visits to the home or as a result of indirect information from other patients and other members of the community a great deal of knowledge and information about the family which is highly relevant from the psychiatric point of view—or, better, from the point of view of total, or integrated medicine. (Some people prefer to use the currently popular term of "psychosomatic medicine.") The doctor learns in the form of privileged communication, or from his direct observations while in the home, what the actual relations of various members of the family to one another and to others in the community are. He learns how the mother feels and treats the father and vice versa, how each of them feels about and treats each of their children, and how each is still tied to, rebellious against, or comfortably independent of, his own parents or the in-laws. Who better than the doctor—except, perhaps, the minister, priest or lawyer—knows the crises of the family's life and its recurrent problems in living? If the physician has some of the equanimity which Osler extolled, if he acquires the wisdom, patience, firmness, which may come with experience, maturity and age, he will be and often is admitted further than into the physical sanctum of the private sick-room of the home. He will be admitted to some of the inner recesses of the family's guarded secrets, confidences and troubles; in short, he will be admitted to their feelings. If over the years he proves himself a worthy confidant, a sturdily optimistic, fair-minded helper in those crises for which his assistance is sought, if he respects himself and all the potentialities and values of each of the persons of the whole family, he becomes gradually invested, by their feelings for him, with a therapeutic power for their welfare which with the chemicals he prescribes or the operations he performs on their bodies may perform even greater miracles of healing than perhaps even he thought were possible.

What I am trying to say in perhaps a roundabout way is that from the point of view of the child's welfare—somatic and psychological—this position and role of the family physician carries with it at least the possibility of all the knowledge necessary to understand the queerest quirk of the child's behavior and emotional state. This position, this relation of the doctor to the family—symbolized by the emotionally charged and mutually meaningful phrases of "our doctor" and "my patients" or "my family"—also has, as all of you very well know, psychotherapeutic potentialities already implicit in it which it may take a psychiatrist or a psychiatric clinic staff weeks, months, or longer to achieve.

In other words, the child is a human organism, at first utterly, and later relatively, dependent upon its parents or other adults, who is always tremendously affected in whatever genetic potentialities he has by not only the impersonal food, protection against extremes of temperature, and against infection or other injury, but also by the totality of the personal, the feeling, environment. As a matter of fact, it is becoming clearer and clearer to most of us that even superior intelligence and the most robust physical inheritance and measures to provide minimal standards of somatic health and care do not necessarily by themselves insure the fullest development and solid integration of the person. The human animal becomes the kind of human being which his immediate personal, familial environment and later social situation permit him to develop into, with his particular, genetically acquired potentialities. If he is wanted, if his parents enjoy having him, and if he finds a stable justice as between himself and his siblings, the young human animal has then a good chance of coming *to feel* as a worthwhile, self-respecting person and member of his family and later of any larger communal group. If his earliest and *necessarily egocentric*, sensual needs of self-exploration, of muscular activity and developing skills are gratified and are not stunted by whatever dark anxieties adults often have, he is not likely at one and the same time to be driven faster and farther than his given maturational stage can take easily, and not likely to become divided in himself, guilty and anxious about some of his bodily impulses and sensations and hence secretly and insatiably longing to return to kinds and quantities of sensation and behavior really denied and prohibited to him earlier. If, on the other hand, he is not smothered by an anxious oversolicitude which has more to do with a mother's or father's secret longing to relive some indulgences denied *them* as children rather than with the child's actual needs for care, for easy warmth of affection, for opportunities for independent trial-and-error learning, and for mastery of his emerging muscular power and dexterity, then the child can also gradually and as a matter of course accept *as his own attitudes*, that is, identify with, such general rules of respect for the feelings and welfare of others as are indispensable to organized, interdependent, social living. If at all

stages of his growth real and basic respect is paid to his rights within the family community; if he is frankly, firmly and honestly dealt with; if opportunities for his play, pleasure and learning are provided as generously as is possible; if his faltering efforts at learning are not derided; if his failures are met with steady sympathy and encouragement and with no trace of the pity which so often hides some gleeful contempt, then he will reflect this experience later in a sturdy, courageous, honest sense of self-respect which will be infused with realistic optimism and a generosity first towards himself and then towards others which will not permit exploitation by others, nor demand ingratiating submissiveness from them. Under such circumstances hateful envy may be minimal, and capacity to benign helpfulness, to collaboration with others of his communal groups, and even more important, a deep ability to love a mate fully may be maximal with neither unnecessary inhibitions in sexual satisfaction nor guilty and obsessional preoccupation with partial eroticisms. What is more, such a child, as a later adult, with neither secret nor repressed longing for childhood satisfactions nor fear of their healthy gratifications, can—*as a parent*—permit *his* child also to live through each developmental period with minimal qualms, maximal security, and thus contribute to his solid and unhurried growth into adolescence and adulthood.

Merely to recount such "ifs" about a child's experience with adults is, I think, sufficient to make my point. It suffices, I hope, to recall to your minds the numerous family situations which you have known and know currently in which many of these "if" conditions were wholly or partially absent. It is probably unnecessary for me to detail some of the typical difficulties which make it almost impossible for parents to provide in their own feelings towards themselves and each other even an approach to these ideals of emotional atmosphere for their child or their children. We all of us know how often parents of the present generation grew up in a home, in a community, in a world quite different from the one they live in now. By different, I mean, of course, one which did not prepare them as well as it might for the present world. *Their* parents may have been born in another part of the world, with another language, with customs different from those in the United States of America, with attitudes towards children and life which did not easily mesh with those of people around them in this country. Their life may have been difficult economically and socially. If these parents of present parents *were* born in this country, they may also have had different attitudes and customs than this country generally had or has now.

In any case, it is not uncommon that the life of present parents during their childhood did not prepare them to live with sufficient equanimity through major, widespread, violently fluctuating economic cycles, perhaps through two world wars, and to the rapidly changing relations of nations of the world to one another with atomic energy as a new sword of Damocles hanging over all. Although intelligent, they may either not have had the opportunity nor learned the persistence to get adequate training of their potential skills to assure them a satisfying vocation and status later. A good many mothers of this generation have had less experience of helping *their* mothers with housework, and they have learned that at least to some extent a woman is almost as good as a man in many occupations and professions. This newer freedom—exemplified by less general horror about their smoking, drinking, going to various schools of higher learning and even participating in many sports and athletics—however, is still only partial and, I suppose, many men still dislike to feel their wives are as smart as they, or could earn almost as much money as they, and sometimes could get along without them. Notice here that these more and more rapidly changing mores of intersexual relations affect both the men *and* the women. Neither is wholly sure what he or she may be or ought to be in relation to the other. Oscillations in both men and women between the old attitudes (man dominantly superior — woman submissively and clingingly inferior) and the new not yet clearly established attitudes of some equality of value as persons of both sexes are frequent. Secret envies, buried but covertly active, hatreds in both for themselves and each other are often laughingly mentioned as the "eternal war between the sexes," but they wreak havoc upon marital happiness, upon adequate sexual satisfaction and, not least, for our problem here, upon successful parenthood.

These changing customs, attitudes and ethics are general conditions, you may say, and not necessarily true of a particular family, and, in a sense, you will be correct. In a specific family history it is more important to learn what happened and is happening to lessen the satisfactions and the security of the parents as adult citizens in a particular community. (In this connection, how frequent is it that families have since their grandparents' day remained in the same community, with their own home, their own familial status?) Has the father the job he enjoys with fairly certain prospects of continued employment, of improvement in salary and status, security for health and old age? Does he worry about how much he owes to his old widowed mother, or does he fret about how much longer he'll be able to stand his mother-in-law around, either in his own home or nearby? Is he tempted to thoughts or deeds of infidelity and does he feel guilty about it because his wife has aged, is too tired, too harried, or too insistently demanding that he continue to baby *her* as well as the children? Does his wife become more panicky at all these more or less subtle signs of loss of his affection, and, in reaction, either naggingly demand more than he can give or become entangled with one or more of her children emotionally who in

turn reacts with a mixture of rebelliousness and neurotic anxiety? Did the parents of either of the parents die at a time critically difficult for either the husband or the wife? Did either the father or the mother immediately upon birth prefer the son or the daughter with corresponding resentful reaction of the rest of the family at their exclusion? Did the second child come too soon after the first one, or at a time when the tension between the parents was highest in their marital history? Was the child only more or less the trick of either parent upon the other to bind the straying one? Or, was the child the result of a sentimentally, but self-deceptively, agreed contract between them to save their marriage after some years of sterility when it was near its ebb; and incidentally, was it urged upon them by friends or even by their doctor? Or, finally, was the child in common parlance an "accident" at a time when neither parent felt ready for it? Again, was the child of the sex opposite to that hoped for and desired by both?

These and many, many other similar questions about the actual, even if hidden, facts and combination of events in the family's life need to be considered as possibilities in the etiology of whatever emotional, behavioral or psychosomatic disorder the child may manifest at a given age. When the child is older and has perhaps lived through some of these unfortunate familial circumstances and events, it may seem as if extrafamilial difficulties in living were more important etiological factors. There may not be enough children of the right age, of the right sex, from the "right kind" of homes to play with. There may be too many children in the class; the teacher may seem too unjust to the particular child. He may not have won some special recognition in school, or he may have failed in some other way. All these extrafamilial conditions and events may be *there* and not only in the defensive imagination of the parents. But close study often, if not usually, reveals that the child's reaction to such events outside the home may still appear excessive, if not partially provoked by the child's own attitudes and personality which he brought to them.

I have been speaking still rather generally, perhaps, about the topic of etiology. Still, in a sense the general principles of etiology of persistent, and rather severe, emotional disorder in childhood of whatever form are no different from those of disorders and diseases which are the result of impersonal factors, that is, of infections, trauma and so forth. In other words, there is no single event or factor which *inevitably* determines the occurrence of a given disorder any more than a given bacterial organism, specific trauma or other non-personal factor always and by itself determines a given sequel in a recognizable organic disease syndrome. Just as a certain quantitative relation between some degree of susceptibility of the organism at a given period of its life and the virulence of the assault upon it of the specific external, environmental factor — bacterium, virus, trauma or whatever — is necessary to produce that reaction of the organism we know as organic disease; so it is with psychiatric emotional disorder. It is the *intensity* of the external interpersonal influences, and the *duration* of their operation as well as the *age* or *maturational phase* of the human organism during which it experiences them which in various combinations *together* produce what one writer has called the "*anthropological*" *variations*,[2] those personality organizations which the rest of us feel and consider as different from ourselves and then call them neurotic, psychotic, psychopathic or just "a bit queer" and write about as "problem children."

This general etiological principle of the period of life, the intensity and duration of the disturbing influences needs perhaps still another word of elaboration. The greatest susceptibility to emotional disturbance is clearly the period of greatest biological and social dependence or helplessness—namely, infancy and early childhood. That period of complete inability to survive and grow without the care and protection of adults is also—contrary to the opinion of many people—the period when conflict and anxiety, tension and uncertainty in the parental or mothering persons have the most disturbing effect. There is now fairly well validated evidence that uneasiness in the mother has a prompt and often severe effect upon the infant's well-being. Because it cannot yet speak and tell us in so many words, it is difficult sometimes to believe that the newborn, the infant or the very young child under one or two years of age can really sense and react to the hidden feelings of its parents who seem so very eager for its welfare. Nevertheless, the various disorders of its physiological functions, from gastrointestinal upsets, skin disorders to irritability and that frequently fatal apathy of marasmus are its way of telling the adult world how it feels it is being treated. I am sure that many, if not all, of you are familiar with these infantile disorders from such writers as Ribble,[4] Spock,[5] Aldrich,[1] and many others. Hence I shall not go into the details. How the tensions of the mothering person, whether in the nursery or the obstetrical ward, or later in the home or elsewhere, are communicated to what seems a still mindless creature, who tends towards sleepy withdrawal except when hungry or cold or on uncertain support is a mystery only to the unobservant. Those who see, sense and grasp how the mother, who struggles against her own more or less unknown but unpleasant and disagreeable impulses towards her child, handles it—either very gingerly, clutching it too tightly or too loosely, and reacts with even greater vacillation to its every whimper, and so on—are not at all mystified at this emotional empathic linkage, as Harry Stack Sullivan[6] calls it, between mother and child. You will notice that I said "those who see, sense and grasp" because if we listen to the mother's story of it we will hear often no word of her subjective state; at most we will hear only her emphatic insistence how careful she has been. She may be able to

speak of her worry, of her anxiety only if she becomes convinced we are sympathetic and not likely to blame or minimize, or deride her feelings about not being an adequate and a good mother. Often we are unable to hear from her any confirmation of our suspicions as to her subjective state in the first or even several interviews. Instead we may hear insistent demands to tell her what is wrong with the child, what should be done for it and so on. If we even gently ask for some details about what happens at times when she feeds it, changes diapers or on other similar occasions, we may evoke an indignantly angry reaction to the effect that *that* has nothing to do with it, that she knows nothing about it, that she follows every detail of the rules of care given her, and, besides, aren't we the doctors and cannot we tell what is wrong by examining the child?

Such reactions of defensive resentment often make the doctor uncertain, uneasy about his hypothesis and half angry at himself and at the mother. If, on the other hand, the mother is the sort who tells more freely what *she* feels, she may finally weep and otherwise be so upset *and ashamed of it* that the doctor may be again embarrassed and feel somewhat helpless at the emotional storm on his hands. In any case, even if the mother's emotional state *is* obvious and perhaps obviously related to the condition of the child, what can one do about it? Often some soothing words, a sedative for the mother or child, or some change in formula or in some other detail of regimen ends the particular episode for the particular doctor who may or may not hear that the child has been taken on subsequent occasions to other, perhaps many other, doctors.

Whatever the factors in her present and past life which contribute to the mother's anxiety in the first year or the first two years of the child's life, they may or may not be sufficiently ameliorated so that the child does or does not experience recurrently or persistently an extremely disagreeable tension within himself when in contact with the anxious mother. If the mother's anxiety is not relieved or ameliorated by what the doctor does or by some change in her life situation or both, it is easy then to see why the child at two or three years of age or later shows some disturbance in emotional and interpersonal development. In general, the more intense the anxiety of the mother—and usually also of the father—the *earlier* in his life and the *longer* the child experiences it, the more severe his personality disorder later and the more likely is he as an adolescent or adult to react with crippling emotional illness to even minor thwartings. The specific exaggerations of interpersonal behavior, the symptoms of the disorder, whether of the neurotically inhibited variety, or of some disturbance in acquiring self-control of egocentric impulses, or of both, depends on the particular rigidities or vacillations of the parental attitudes. The child usually, if not always, mirrors the personality problems of the parents; his symptoms and his behavior reflect how he has been treated, which generally also reflects how the parents treat themselves. This is a generalization which may be difficult to confirm in any given clinical instance only if we do not spend an equal amount of time, patience and skill in learning to know the parents as well as the problem child, or if we prefer some theory about obscure genetic, constitutional factors, and disease of the brain and glands as being the preeminently important determinants of deviations of personality development.

This very brief review of etiology brings us to the problem of therapy. Therapy by the specialists generally consists of talking, of interviews with one or both parents *and* with the child, unless he is between two and a half and seven or eight years of age, in which case the therapist and child spend their time together in a play room. Whether the frequency of the meetings between the child and his therapist and those between the parent or parents and their therapists are the same, or whether the child is himself the object of most or of all the therapeutic attention, varies. In private treatment (especially psychoanalytic treatment) the child may have roughly one-hour sessions several times a week for months with the child analyst while one or both parents are in psychoanalytic treatment with other analysts, or are seen in occasional conferences with the psychoanalyst of the child. In many, if not perhaps in most, psychiatric out-patient clinics for children, in which the therapeutic staff may not have been trained psychoanalytically, the traditional division of labor is that the psychiatrist sees the child in the playroom or office in which there are such toys as dolls, doll furniture, crayons and paper, plasticene, finger paints and so forth, while the clinic psychiatric social worker sees the parent, most often the mother, in interviews. The sessions in such clinics are usually less frequent than in psychoanalytical treatment, generally about once a week. There are, here and there, some differences of practice. In some clinics the clinical psychologist—the third member of the professional clinical team—may also engage in some therapeutic interviews in addition to his traditional, clinical job of psychometric and other diagnostic testing. In other clinics, if the staff has more than one psychiatrist and they are trained for psychotherapy, the child and parent may be both treated by psychiatrists. This is especially true if the problem is severe. There is still considerable debate in this field as to whether the interviews with the parent are an essential part of the therapy, especially when conducted by a social worker, or are especially then to be called "casework." In a few instances one hears of efforts by one and the same therapist — especially in private practice — to see therapeutically both the child and parents—at different times, of course.

I hardly know whether to include some institutional types of attention to problem children as therapeutic in the strict sense. Various homes and special schools, especially when small and operated privately, give some domiciliary care and training

to children with various emotional and/or intellectual handicaps. Hospital wards for children, residential treatment centers, must also be mentioned under children's psychiatric facilities, although they may vary in their theoretical orientation and hence in forms of therapy. Hospital wards for children are either parts of urban psychiatric hospitals, often teaching and research institutions, such as the ward at Bellevue Hospital in New York, at the Illinois Neuropsychiatric Institute in Chicago, or at the Langley Porter Clinic in San Francisco, or are special units on state hospital grounds such as at Camarillo and Napa State Hospitals in California. Whether the parents also receive therapeutic attention from the staff of such institutions depends upon many factors, such as the size and training of the staff, the number of children that must be cared for and the possibility of parents being able to come regularly enough and frequently enough to the hospital.

If we leave out of discussion the insulin, electroshock therapies with which I have no experience in the case of children's disorders—although I understand they are performed in various places—we may very briefly review the principles of psychotherapeutic work in child psychiatry. I say psychotherapeutic because the so-called "play therapy" is perhaps also more properly called psychotherapy. As one of my colleagues[2] once wrote, many people play with children, but they do not for this reason do any therapy. Play is for the child merely a partial substitute for speech in the child-psychotherapist emotional interaction and communication. A child, when sufficiently eased, in time, of his uncomfortable feelings in the presence of the trained adult therapist, may express some of his conflicting attitudes in play more spontaneously than in speech, just as the adult may be more able to do it in what is technically known as "free-association." In either case, whether with adult or child, with speech or with both speech and play as the mode of preferred communication between them, the patient and therapist begin what hopefully develops into an emotionally significant relationship. If this does develop—and whether it does or not depends upon many factors such as the frequency of the meetings, the duration of the therapy and, not least, the special training, skill and capacity of the therapist to understand the feelings and conflicts of children—if it does develop, there is then some chance that the child may begin to *feel* differently about himself, first in the presence of, and in relation to, his therapist, and later more generally with, and in relation to, most other persons in his life. This different feeling about himself in favorable or more successful instances is in the direction of sturdier self-respect, more realistic and more tolerant self-esteem for his actual assets and limitations, greater capacity to permit himself to *feel* whatever he feels in any situation but with a greater discrimination and greater fairness to himself and to others as to how he will express these feelings in action. In short, one hopes for at least some reduction—if not resolution—of his conflicts and self-destructive impulsiveness.

The details of the mutual work of both patient and therapist and of such phenomena as the "transference" which may eventuate in some such result cannot be dealt with cursorily. I wish, however, briefly to add a word about my own theoretical and practical inclinations with respect to the contribution of the therapy of parents to this possible therapeutic result in the child's feelings, attitudes and behavior. What seems to be clear to me both theoretically from what I have said previously and validated in a large measure in my own clinical experience is the following: As I have emphasized already, children, although individual human beings, are inevitably at the same time members of the family, their own biological family or another socially more or less their own. They are, in more impersonal terms, partially autonomous, component units of a larger, an organic system or unity. I think there is sufficient evidence also to say that the kind of persons or social entities they are or become results in a great measure from this fact. I find it convenient and useful, therefore, to consider their behavior, feelings and attitudes—their personality organization, in other words—as expressive of the kind of family social unit or system of which they are a part. To repeat what I said previously, the way they feel and act reflects how they have been treated by the adult persons who care for them. How these persons have treated them expresses or reflects how these adults basically feel towards themselves. Hence, an emotionally disturbed child to me indicates unhappy parents in the same way that a sick organ indicates or expresses a sickness of some sort or degree of the entire organism. In the case of the sick organism we know as physicians that it may not be enough — if it ever is — to treat only the sick organ. As a matter of fact, in more and more diseases we are learning that treating the entire organism is often more important than the sick organ, and now and again the most direct way towards restoration to health of this sick organ.

I am sure I need not labor the analogy further. If you review your own clinical experience from this point of view, I am rather confident you will find confirmation for the statement that helping a parent or *the family as a whole* to greater happiness, integration, mental health or however you wish to term it, is often an important and at times the most direct way to help an unhappy child. I must add immediately two things: First, we may at a certain juncture in the life of another person be unable either to do much or to do anything at all to help him feel and live more contentedly; and, second, to say that helping a parent is important does *not* mean that direct help to the child is unimportant or unnecessary. It is —as in the case of the organism with an obviously very sick organ—a matter of flexible, clinical judgment, of available therapeutic armamentarium, of time, of severity of disturbance in all parts of the

system, and of the easiest avenue of approach. In terms of the family with a problem child, it is his age, the severity and chronicity of his disorder, as well as the therapeutic availability of his mother, father or their substitutes, and the time, skill and personnel which together determine whether all three will receive therapeutic attention, or only two or one of them.

What constitutes "therapeutic availability" needs another bit of explanation. I mean by this term not merely whether the father as well as the mother, in addition to the child, have the time and there is some financial possibility of giving each of them some therapist's time, but even more important, whether any one, two or all three of them are basically more or less ready and more or less *willing* even to begin to work out their individual and therefore common problems and conflicts with a therapist.

In any case, it is certain that any change, whether towards integration or the obverse in any component part or member of the familial social system will affect other parts or members or the entire unity. And this is what we see clinically in child and father if mother only is helped to feel a more solid self-esteem or in any other combination. Clearly, if both the parent or parents as well as the child can be given assistance simultaneously, there is — other things, such as therapeutic skill and time, being equal—greater chance of quicker or more thorough therapeutic results. By the same token, the more severe the disorder, the more likely is some positive therapeutic result to follow the more total treatment of the entire family.

REFERENCES

1. Aldrich, C. A. and M. M.: Babies Are Human Beings, New York, Macmillan Co., 1938.

2. Erikson, E. H.: Observations on Sioux education, J. Psychol., 7:101-156, Jan. 1939, especially page 133.

3. Gitelson, M.: Direct psychotherapy of children, Arch. Neurol. and Psychiat., 43:1208-1223, June 1940.

4. Ribble, M.: The Rights of Infants, New York, Columbia Univ. Press, 1943.

5. Spock, B., & Huschka, Mabel: Psychological Aspects of Pediatric Practice, Pract. Libr. Med. & Surg., 13:757-808, New York, Appleton-Century Co., 1938.

6. Sullivan, H. S.: Conceptions of modern psychiatry, Psychiatry, 3:8-9, Feb. 1940.

7. Sullivan, H. S.: Therapeutic investigations in schizophrenia, Psychiatry, 10:124, May 1947.

Epinephrine Hand Nebulizer in Asthma

Technique of Use, Clinical Aspects

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SUMMARY

It behooves the physician seeking relief for asthmatic patients not to be casual about the epinephrine hand nebulizer and the manner in which it is used. Patients who claim to get no relief from the nebulizer should be asked to demonstrate their technique. If the nebulizer produces a hardly visible mist, it should be discarded. For many patients, the goal in spraying by hand must be the production of more or less continuous and voluminous aerosol, regardless of the phase of respiration, in order to effect relief. If the respiratory pattern has not deviated too far from normal in rate and depth, inhalations may be carried out in courses or cycles of about a half-minute duration and spaced a few minutes apart. If the respiratory pattern is abnormal during the act of spraying, it must be corrected.

Inhaled epinephrine aerosols as constituted today appear to be somewhat irritating to the mouth, throat, and upper portion of the pulmonary tract of some persons, but it has not been convincingly demonstrated that serious and permanent damage to the lower respiratory tract of humans can occur from long-continued use of inhaled epinephrine.

ALTHOUGH the general procedure involved in using the epinephrine hand nebulizer is readily grasped by the average patient, the actual performance in many instances leaves much to be desired. Physicians for the most part assume that patients will acquire proficiency either from experience or from the printed directions accompanying the instruments when purchased. However, the latter source of information is frequently far from adequate and most patients are fearful of self-experiment with such a potent drug. The result is that many an asthmatic patient fails to obtain relief solely because of poor technique, a fact pointed out by one of the popularizers[5] of this method of therapy. Despite this situation, no detailed discussion of the technique of use of the hand nebulizer has appeared in the literature.

Recent interest on the part of investigators in the development of other devices[8, 9, 14] for producing inhalant materials may possibly soon lead to obsolescence of the epinephrine hand bulb nebulizer. Until such time as this occurs the present communication may prove to be helpful to the practitioner who sees only an occasional asthmatic patient and may therefore not be aware that pitfalls in the technique of use of the hand nebulizer can unnecessarily rob certain patients of relief.

What follows does not apply either to patients in status asthmaticus or to those who respond so readily to one or two inhalations that they absorb an adequate amount no matter how they use the nebulizer. It pertains rather to a considerable group of patients who fall between these two extremes, who are generally ambulatory but subject to asthmatic seizures of moderate to severe intensity and of variable frequency, and in whom the difference between success and failure in obtaining relief by inhalation depends on inhaling a certain minimal quantity within a relatively short period of time.

The commonest error committed by patients in this group is to attempt to synchronize inspiration with manual compression of the bulb. This error is furthered by the many vendors who sell the nebulizers packaged with their own particular trade name for what is essentially a 1:100 solution of epinephrine hydrochloride. Typical directions in such a package instruct the patient: "Hold the nebulizer outlet inside the mouth, and with mouth open squeeze the bulb while inhaling. Do not pump while exhaling. Only a few inhalations are necessary. If symptoms are not relieved in a few minutes, the inhalations may be repeated." What usually happens in following such directions is that the patient begins to inspire so far in advance of compression of the bulb that inspiration is almost completed before any epinephrine enters the lungs. For the patients under discussion here a larger intake than can ever be obtained by this method is necessary.

Since the aim of therapy is to produce relief, not to economize on epinephrine, it is advisable at all times to keep the mouth of the patient so full of the aerosol that the material can be readily sucked down into the lungs from the very beginning of inspiration. This can be accomplished only by rapidly repeated forcible compressions of the bulb, regardless of the phase of respiration. In this way, the conditions of constant flow obtained by attaching the nebulizer to an oxygen tank are approximated.

If the respiratory pattern has not deviated too far from normal in rate and depth, the patient may inhale a considerable number of times before he stops spraying. Comparative freedom from side-effects is one of the advantages offered by this route of ad-

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ministration. However, a method of minimizing inhalation of needless excess is to caution the patient not to inhale more than ten to twelve times, or for longer than a half minute at a time, then to wait for a few minutes to see what degree of relief will ensue before repeating the course of inhalations. As many as five or six successive half-minute courses, spaced a few minutes apart, may then be attempted before it can be concluded that relief by this method is not obtainable.

The degree of relief attained by this technique will be found to run a gamut from complete relief after a few initial inhalations to only partial relief or no relief even after six courses or more. For those who respond slowly, the later courses may bring about a greater degree of relief than the first or second, but the degree of relief is as a rule maximal after five or six periods of inhalation, so that if relief is at this time only partial or absent, further spraying is generally useless for the time being.

Many patients unconsciously alter their breathing pattern when nebulizing. Some, on the one hand, will exaggerate both rate and depth of respiration. Patients in this group who cannot be taught to approximate the normal must be cautioned to restrict themselves to no more than three or four exaggerated respiratory excursions at a time during each course lest symptoms of hyperventilation develop. Other patients, on the other hand, will unaccountably diminish respiratory excursions to a notable shallowness, almost holding the breath while spraying. Patients in this group should be taught either to convert to a normal rate and depth or to adopt the pattern of a few forced, exaggerated respirations per spraying cycle as in the preceding group.

Some persons find it almost impossible at first to avoid synchronizing nebulization with inspiration. They apparently lack a ready facility to carry on a hand compression of the bulb as a separate act by itself at a rate different from the respiratory rate. In these circumstances it is best for some other member of the family to work the hand bulb until such time as the patient can learn to do this properly for himself.

FAULTY INSTRUMENTS

In spite of close attention to the preceding details relative to the respiratory pattern, failure may yet ensue if the nebulizer is not an efficient one. It is unfortunate that one instrument which is designated as a vaporizer and is widely sold today under the name of a nationally known pharmaceutical house delivers a mist so meager in volume that a high percentage of patients, in the author's experience, fail to obtain relief with it. This is in accord with the similar experience of Harsh[7] with this instrument. Patients using this model who are certain they cannot obtain relief from inhaled epinephrine are agreeably suprised with results obtained with a nebulizer producing a more voluminous mist.

EFFECT ON MUCOSA

Since what is being advocated here is the liberal use of nebulized epinephrine during an asthmatic paroxysm to ensure that maximum benefit may be attained, the question of injury to the respiratory mucosa arises.

Injury has been experimentally produced in animals by long-continued exposure to epinephrine mist. Fox[3] sprayed rabbits intranasally with a 1:1,000 solution of epinephrine hydrochloride over a three-month period and on sectioning the maxilloturbinates found that the mucosa showed increased leukocytic infiltration with formation of intraepithelial abscesses and areas of denudation of the epithelium. Galgiani[4] and co-workers used the 1:100 dilution as a spray for a few months in cats and rabbits. In some of the animals, but not all, loss of tracheal cilia and desquamation of the tracheal and bronchial epithelium with inflammatory changes in the sub-mucosa were noted. In one human subject moribund from tuberculosis and subjected to frequent spraying in the 48-hour period before death, similar changes were demonstrable postmortem and were attributed to the epinephrine.

It is curious, however, that despite widespread use of the nebulizer since its popularization[6,11] some years ago, severe injury of the lower respiratory tract due to frequent inhalation has not been reported in humans save very recently by Benson and Perlman.[2] These observers reported a few cases in which they felt that death had been caused by excessive use of 1:100 epinephrine for relief of asthma. They postulated a sequence of events in these instances whereby damage to the respiratory mucosa became severe enough to lead to infection with subsequent formation of occluding plugs, anoxia, and death. Unfortunately for their thesis, and as the authors themselves admit, the pathological changes they describe (loss of cilia, epithelial metaplasia and desquamation, cellular infiltration of the subepithelial layers) were described at postmortem examination of asthmatics before the era of epinephrine inhalation. To ascribe these changes to epinephrine and to claim an increased mortality therefrom is at variance with the experience of observers [5,12,13] who have administered aerosolized epinephrine to innumerable patients without any seeming ill effects, or at any rate without any effects that have hitherto been ascribed to inhalation therapy. Benson and Perlman believe that the pulmonary changes in question constitute a pattern of injury reproducible by any irritant and the occurrence of this pattern in asthmatic patients before the widespread use of epinephrine inhalation cannot discredit the role of the drug in the production of such changes also.

It cannot be denied that some degree of irritation does occur in the mouth and throat in a fairly high percentage of patients.[5,6,10] Patients frequently complain of dryness and/or burning in the throat area following even short-time use of the spray. Transient

mild irritation of the lower bronchial tree may also be a factor in the initial increase in coughing which follows immediately after inhalation in many instances, and which is quite helpful in dislodging and bringing up mucus. (It should be kept in mind, however, that later bouts of coughing may be due to stimulation of sensory nerve endings by loosened plugs of mucus. It is well, incidentally, to caution patients that a pinkish stain which may appear in material that is coughed up is due to oxidation of the epinephrine and not, as many frightened patients assume, to blood. The possibility of hemoptysis must nevertheless always be kept in mind and in case of doubt appropriate procedures instituted to ascertain the nature of the stain.)

MINIMIZING IRRITATION

One simple method of minimizing irritation is to direct the patient to rinse the mouth after each session of spraying.[6] Lockey[10] pointed out that irritation may also be minimized by adding glycerine to the epinephrine solution to a final concentration of 5 per cent. Other advantages accruing from glycerine, such as stabilization of the particle size of the mist, have been pointed out by Abramson,[1] who favors a 25 per cent concentration, and concurred in by Harsh[7] who pointed out still further advantages such as a bacteriostatic and a wetting effect.

In most instances any irritation produced by the aerosol is transient and subsides either because the interval between asthmatic seizures is sufficiently long, or because the average patient with localized symptoms of any severity will desist from further use of the nebulizer until the symptoms have disappeared. There is thus a distinct difference between humans who naturally bring their defense mechanisms into play and animals who are not permitted to do so, as in the experiments mentioned. Also, species and individual differences may be of importance, since every allergist encounters patients who use unbelievably large quantities of epinephrine by inhalation and by injection daily for months and years without any apparent ill effects.

In certain instances, however, asthma is persistent enough, and severe enough, so that the temptation to continued use despite symptoms of irritation is overwhelming. It is in these instances that the possibility may arise of serious damage to the lower respiratory tract from long-continued inhalation. In such circumstances, if the nebulizer is only minimally effective it may be simple enough to prohibit its use and substitute other measures of equal or greater efficacy. Some patients in fact learn by experience that the spray suffices only for the milder attacks and automatically discard it for other measures for the more severe attacks.

The advantages of this method of therapy are ease of application, quickness of response, comparative freedom from side-reactions, and, to a degree depending on the severity of the asthma, comparative freedom from home confinement by reason of portability of the nebulizer. Many a patient's life has been made bearable through the use of this simple contrivance. Given such a situation—but provided, of course, that similar relief cannot be obtained in any other way—the propriety of denying to the patient the benefits of inhaled epinephrine is open to question. One must look askance at a logic which attaches utmost importance to protection of the respiratory tract from possible permanent damage which might accrue over a long period of time and precludes all consideration of the patient's general comfort and well-being from day to day. In this connection the recently expressed opinion of an asthmatic patient who is himself a physician[15] is illuminating: "Not being able to see my bronchial mucosa I am not worried about [the effect of the spray on] its possible thickness or the inactivity of its cilia. I am, however, able to carry out a full day's work. . . . If my life has been shortened by using adrenaline sprays, at least I shall have had more hours of useful activity on earth than I should otherwise have had."

It would seem, then, that with respect to this problem of long continued use of the hand nebulizer there is at present no substitute for the exercise of judgment by the physician in each individual instance. One comes thus to the same conclusion as did Galgiani[4] and his co-workers who despite the results of their animal experimentation and despite being convinced that considerable local damage may result stated: "The clinician would therefore seem to be under the necessity of deciding in each individual case whether the gain in convenience of medication by inhalation is great enough to justify the possible production of added pathologic changes."

OTHER DISADVANTAGES OF USE OF HAND NEBULIZER

It is necessary to point out that damage to the respiratory tract is not the only objection that can be advanced against the use of the nebulizer. There is a measure of correctness in the view held by some allergists that if an asthmatic patient gets satisfactory relief by this method without ever having gone to a physician, or shortly after he is introduced to this technique by a physician, he may stay away from medical observation and thus the cause of the asthma may never be determined. This possibility is enhanced by the present widespread and unregulated over-the-counter traffic in the sale of both nebulizers and solution. If the onset of asthma is in adult life, and symptoms remain moderate in degree without leading to organic changes in the cardiopulmonary apparatus, the matter may be of no consequence. In the case of a child, however, failure to seek proper medical care may lead to undesirable consequences.

It is true, furthermore, that some patients use the nebulizer with unncessary frequency, at the slightest sensation of "pressure" or "heaviness" in the chest, without waiting to see whether or not their symptoms will subside. Such patients may build up a neurotic dependence upon having the nebulizer ever

at hand. Illustrative of an interesting psychosomatic aspect of asthma, it is conceivable that a few individuals in this group may at times develop asthma solely as a fear-conditioned reflex should they perchance unexpectedly find themselves without the nebulizer in their possession. Some physicians, for any or all of these reasons, refuse to allow their patients to use a nebulizer. But the solution of these problems should not lie in interdicting the use of the nebulizer by those who desperately need it merely because some may use it unwisely and without supervision.

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REFERENCES

1. Abramson, H. A.: Aerosol therapy of the lungs and bronchi with special reference to penicillin and hydrogen peroxide, Bull. New Eng. Med. Center, 8:97, June 1946.

2. Benson, R. L., and Perlman, F.: Clinical effects of epinephrine by inhalation, Jour. Allergy, 19:129, March 1948.

3. Fox, N.: The chronic effect of epinephrine and ephedrine on the nasal mucosa, Arch. Otolaryng., 13:73, Jan. 1931.

4. Galgiani, J. V., Proescher, F., Dock, W., and Tainter, M. L.: Local and systemic effects from inhalation of strong solutions of epinephrine, J.A.M.A., 112:1929, May 13, 1939.

5. Graeser, J. B.: Inhalation therapy of bronchial asthma, J.A.M.A., 112:1223, April 1, 1939.

6. Graeser, J. B., and Rowe, A. H.: Inhalation of epinephrine for the relief of asthmatic symptoms, J. Allergy, 6:415, July 1935.

7. Harsh, G. F.: A comparative study of commercial nebulizers, Annals of Allergy, 6:534, Sept.-Oct. 1948.

8. Krasno, L., Karp, M., and Rhoads, P. S.: Inhalation of penicillin dust, J.A.M.A., 138:344, Oct. 2, 1948.

9. Krasno, L. R., Grossman, M., and Ivy, A. C.: Norisodrine dust inhalation for asthma, Science, 108:476, Oct. 29, 1948.

10. Lockey, S. D.: Inhalation of oxygen and 1:100 epinephrine hydrochloride plus five per cent glycerin for the relief of asthmatic attacks, J. Allergy, 14:382, July 1943.

11. Matzger, E.: Epinephrine by inhalation for the relief of attacks of bronchial asthma, Calif. & West. Med., 43:226, Sept. 1935.

12. Richards, D. W., Barach, A. L., and Cromwell, H. A.: Use of vaporized bronchodilator solutions in asthma and emphysema, Amer. Jour. Med. Sci., 199:225, Feb. 1940.

13. Segal, M. S.: J. Allergy, 19:278, July 1948.

14. Taplin, G. V., and Bryan, F. A.: The use of micronized therapeutic agents by inhalation, Annals of Allergy, 6:42, Jan.-Feb. 1948.

15. Wingate, P.: Asthma and the inhaler, Brit. Med. J., 1:226, Jan. 31, 1948.

CASE REPORTS

Coccidioidomycosis of the Genital Tract

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TWO patients who had a rare type of fungus infection of the genital tract were observed recently. As nearly as can be determined there are no previous reports of cases in which an isolated genital lesion was the only indication of metastasis of coccidioidal infection.

In one of the two cases, an incorrect diagnosis of tuberculous epididymitis had been made previously. Although microscopic examination of tissue removed at operation elsewhere had shown lesions which had been thought to be tuberculous, the subsequent isolation of Coccididoides immitis revealed the true cause. In the second case, the diagnosis of coccidioidomycosis was made on the basis of the history and serological tests prior to operation.

The term "coccidioidomycosis" should not be confused with "coccidiosis." The former refers to infection caused by the fungus Coccidioides immitis. "Coccidiosis" refers to an infection by a sporozoan parasite under the order Coccidia which affects mainly poultry and small animals.[2]

CASE REPORTS

CASE 1: The patient, a white male 42 years of age, entered the hospital December 31, 1947, complaining of an open wound in the right inguinal region. Four months previously he had noted a painless swelling at the lower pole of the right testicle. The swelling had gradually enlarged and become acutely painful. After parenteral administration of penicillin, the swelling and pain had subsided. Because the epididymis remained indurated, however, the right testicle had been explored six weeks prior to admission to the Veterans Administration Hospital. At that time the affected testis and epididymis had been removed. Results of pathologic examination had been reported to indicate tuberculosis of the epididymis.

The wound had healed superficially, but remained indurated, and three weeks after operation it separated along the line of incision, and a granulomatous process developed in the surrounding skin and subcutaneous tissues. During the three weeks before the patient came under the care of the authors, the wound had shown no signs of healing.

The patient's home was in Los Angeles, and he had traveled extensively throughout Southern California during the previous 16 years. Seventeen months prior to the onset of illness, he had made a two-day hunting trip to Taft in Kern County. Within ten days after the trip, acute illness, which was manifested by chills, fever, headache and pains in the chest, developed. The diagnosis was pneumonia, and the patient remained in bed for ten days. Treatment consisted of parenteral administration of penicillin. The symptoms gradually subsided and within a month the patient had apparently regained normal good health.

On the patient's admission to the Veterans Administration Hospital, the temperature was persistently elevated to 100° F. The right scrotal and inguinal areas were occupied by a granulating mass about 6 cm. in diameter. There was deep induration, and fluctuation was elicited around the stump of the spermatic cord, felt in the upper portion of the scrotum. The area of fluctuation extended high into the inguinal region. The left testis, epididymis, and spermatic cord, both seminal vesicles and prostate were normal to palpation. The prostatic secretion was microscopically normal. The remainder of the physical examination did not reveal abnormal findings.

A differential leukocyte count showed eosinophilia (5 per cent eosinophils) but was otherwise normal. The sedimentation rate was 25 mm. in one hour (Westergren method). The urine did not contain pus cells, red blood cells, or bacteria. X-ray study of the chest showed a mass of soft tissue density, 2 cm. in diameter, in the region of the left hilum (Figure 1). The lung fields were otherwise clear. Intravenous urograms and skeletal roentgenograms were interpreted as being normal. Intradermal tests showed a sensitivity to tuberculin in dilutions of 1:1,000. Gastric washings and repeated cultures of the urine were negative for tubercle bacilli.

The clinical picture remained unchanged during a week of observation. The clinical impression was that the condition was pulmonary tuberculosis and tuberculosis of the stump of the right vas deferens with secondary infection and abscess formation. Incision and drainage of the fluctuant area in the right inguinal region, one week after the patient entered the hospital, yielded approximately 60 cc. of thick pus and caseous material. Generous portions of the granulomatous tissue were excised for biopsy, but no attempt was made to debride the wound completely. The edges were left widely separated with a packing of iodoform gauze.

Postoperatively the patient's temperature promptly returned to normal. There was little drainage from the wound (Figure 2).

A heavy growth of fungus was cultured from pus obtained at operation (Figure 3). Other forms of bacteria were not found on smear or culture. Pathologic examination of the granulomatous tissue showed spherules of Coccidioides in well-defined tubercles (Figure 4). The original sections of the epididymis were reexamined and spherules were not found, but on additional sections, coccidioidal endospores could be seen in abundance. Cultures of urine and spermatic fluid made shortly thereafter produced heavy growths of Coccidioides.

Arthrospores of cultured fungus were injected into the testes of guinea pigs and acute purulent orchitis developed; endospores were identified and recultured.

Serological tests* were made on the 23rd hospital day.

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*By C. E. Smith, M.D.

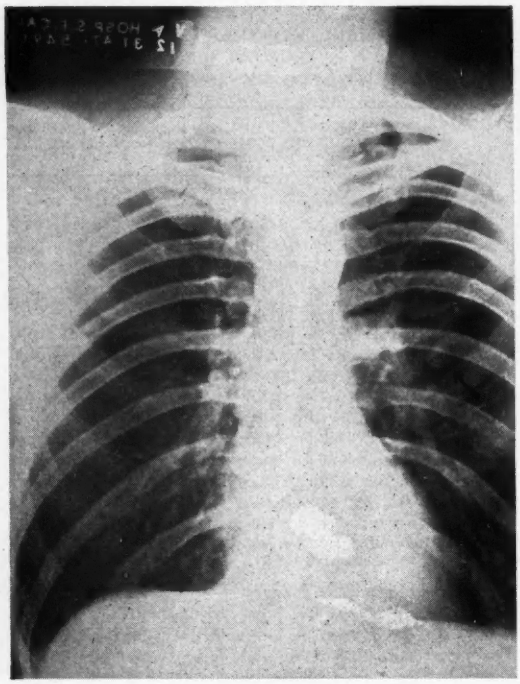

Figure 1.—X-ray film of chest. Arrow points to lesion in left parahilar area, considered to be the primary focus of the coccidioidomycosis.

The result of a complement-fixation test for coccidioidal infection was strongly positive, whereas the precipitin test was negative. Intradermal injections of coccidioidin showed a slight sensitivity in dilutions of 1:10. The findings were interpreted as being compatible with a nonprogressive single metastatic lesion due to Coccidioides immitis and he considered that the low complement-fixation titer indicated a good prognosis.

Local application of tyrothricin ointment was the only additional treatment the patient received.

Thirty days after operation, the induration surrounding the wound had receded and the skin edges were beginning to grow in. Cultures of material from the wound still grew Coccidioides in great abundance. The patient was afebrile, ambulatory and gaining weight. The sedimentation rate had fallen to 4 mm. in one hour. A differential leukocyte count showed only 1 per cent eosinophils. There was no change in the results of serological tests.

The patient was discharged from the hospital two months after operation. By that time the wound had healed except for a small, granulating area, less than 1 cm. in diameter. Cultures of material from the wound, urine, and spermatic fluid still grew a few colonies of Coccidioides. On follow-up, 16 months later, the patient was in excellent health, but a few Coccidioides could be grown on culture of spermatic fluid. The wound was completely healed.

The patient is being observed at frequent intervals. Radical treatment, such as further operative procedures, is not planned unless indications arise. Although the growth of Coccidioides from the spermatic fluid indicates that the infection is still active in the genital tract, there are no obvious gross changes in the seminal vesicles, prostate, or remaining testis and epididymis. Encouraging evidences that the disease is limited are the healing of the wound, the gain in weight, a normal sedimentation rate, the negative reaction to precipitin test, the low titer of the positive complement-fixation test, and a normal blood count.

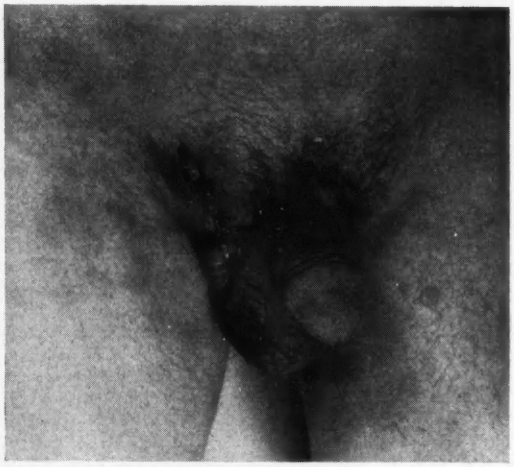

Figure 2. — Lesion in right inguinoscrotal area four weeks after incision and drainage.

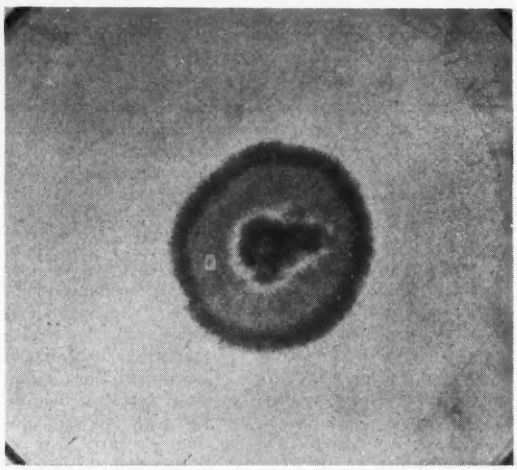

Figure 3.—Coccidioides immitis culture on Sabouraud's agar.

* * *

Case 2: The patient, a 31-year-old white male, entered the hospital on October 28, 1948, complaining of enlargement of the left testicle for two years. Five years prior to entry, when he was in the Mojave Desert, a dry, nonproductive cough and low-grade fever had developed. After a diagnosis of pleurisy with effusion, thoracentesis was carried out repeatedly, but tubercle bacilli were not found. Result of a tuberculin skin test was positive, but an etiological diagnosis was not made.

Two years before admission the patient noted a sudden painful enlargement of the left side of the scrotum; this subsided within several weeks, leaving a residual non-tender swelling. The enlargement remained unchanged until 15 days prior to entry when the patient received a blow to the left testis. This was soon followed by a painful swelling and the occurrence of two openings over the left side of the scrotum, which drained a foul-smelling purulent mate-

rial. Again the mass decreased to its former size, but drainage continued.

Physical examination at the time of admission to hospital was of interest only as concerned the genitalia. There was pronounced enlargement of the superior pole of the left epididymis with lesser enlargement of the inferior pole and adjacent testis. A fluctuant area which transmitted light lay anterior to the testicle. The surrounding scrotal skin was moderately indurated and the contents were fixed to the lateral scrotal skin at the site of two small fistulae. The vas deferens felt normal. The right testicle was normal. The prostate was of normal size, contour and consistency; the secretion was normal. The seminal vesicles were not palpable.

The urine was normal. The sedimentation rate was 32 mm. in one hour (Westergren). A differential leukocyte count showed 4 per cent eosinophils. Ejaculate culture was negative for Coccidioides. Serological tests for coccidioidal infection showed positive complement-fixation and negative reaction to precipitin tests. An x-ray film of the chest revealed no abnormalities. Reaction to a coccidioidin skin test was strongly positive. The result of a tuberculin skin test was negative.

Following a diagnosis of coccidioidomycosis of the left epididymis and testis, left epididymo-orchiectomy was performed. The entire testicle, adjacent spermatic cord, attached sinuses and skin were removed without opening the tunica vaginalis testis (Figure 5*A*). The vas deferens was separately ligated and implanted subcutaneously.

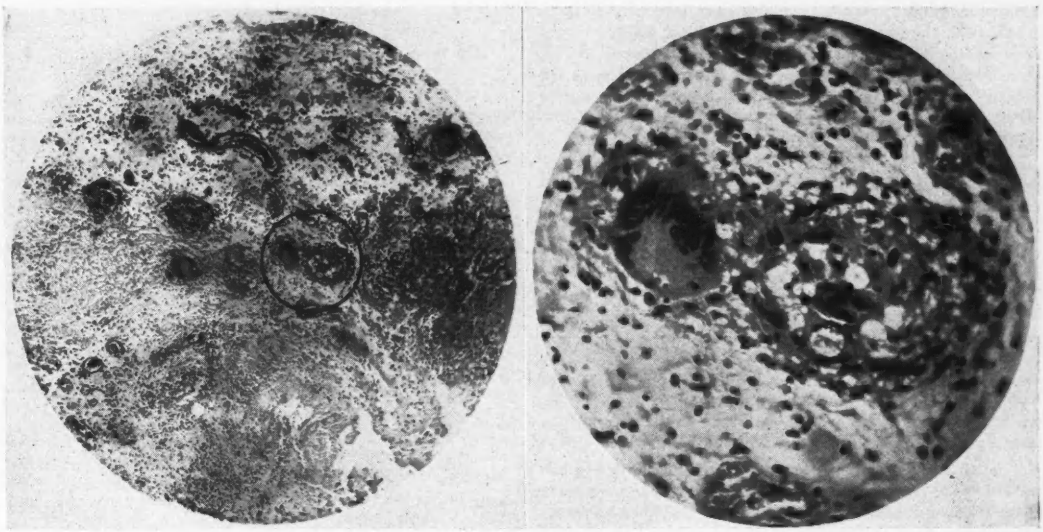

Figure 4.—*Left,* granulomatous lesion in the epididymis (Case 1). Note tubercles, giant cells, and caseation, closely resembling the microscopic picture of tuberculosis. *Right,* Characteristic spherule of Coccidioides immitis in tubercle with a multinucleated giant cell.

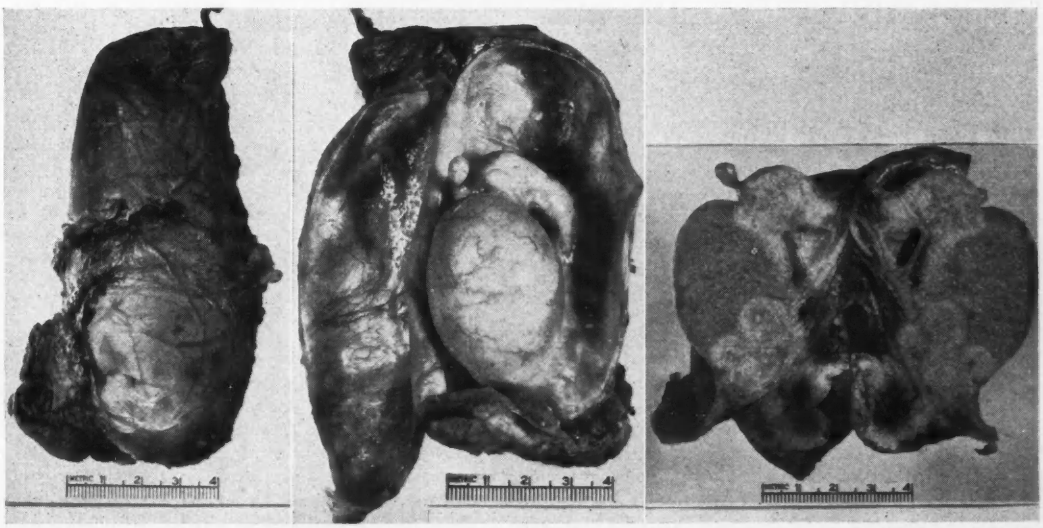

Figure 5.—*Left,* intact hydrocele and attached skin containing two small sinuses (Case 2). *Center,* opened tunica vaginalis. Note enlargement of globus major of epididymis and appendages. *Right,* diffuse granulomatous involvement of epididymis and testis as seen on section.

Pathological examination showed a smooth-lined hydrocele sac filled with brown fluid. The epididymis and testis were partially replaced by granulomatous material (Figure 5). On microscopic examination, a chronic granulomatous process containing many double-contoured refractile bodies of Coccidioides immitis was found.

The postoperative convalescence was uneventful, and the wound healed rapidly by primary intention. Subsequent serological tests for coccidioidal infection showed a fall in titers coinciding with extirpation of the only proved metastatic coccidioidal lesion.

DISCUSSION

It is generally accepted that the initial infection in coccidioidomycosis occurs when arthrospores of the fungus are inhaled from dust and establish a primary lesion in the lung. At this site the organisms may be walled off, as in primary tuberculous infection, or lead to generalized dissemination. Dissemination takes place soon after or coincident with the primary infection, but occurs in only about 1 per cent of clinically manifest infections in white males. Dissemination is more frequent in dark-skinned races.[3]

Forbus and Bestebreurtje[1] reported the distribution of lesions found on necropsy in 50 cases of disseminated coccidioidomycosis. In 60 per cent of these cases, gross renal lesions were evident. In only 6 per cent were lesions found in the prostate, and these were evident only on microscopic examination. Lesions were not observed in any other organ of the urogenital system.

Since dissemination generally occurs within three to six months after the initial infection, the first of the two cases here reported is unusual in that evidences of genital involvement did not appear until after a latent period of 17 months. The second case is remarkable in that the genital infection must have been dormant for two years before the patient sought medical treatment of the scrotal swelling.

The disease is known to be extremely infectious when human beings or animals are exposed to the arthrospores from infected culture plates or dust, but as far as is known the disease is not transmitted from person to person, and isolation is thought to be unnecessary.

The cases reported here suggest the possibility of intraperitoneal implantation of coccidioidal endospores. Since the ejaculate in the first case was heavily contaminated, the question arises whether infectious material could be carried into the peritoneal cavity of the female by spermatozoa after sexual intercourse and there find a suitable habitat for growth. However, this is unlikely because the disease cannot be transmitted in the endospore stage. Unfortunately, the first patient's wife refused examination because of religious tenets. The wife of the second patient was tested, despite the fact that Coccidioides was not cultured in the husband's ejaculate. Results of a skin test were negative and an x-ray film of the chest showed no abnormality.

The present treatment of coccidioidal infections consists of measures to build up the patient's general condition. Although specific medication of any value has not yet been reported, extirpation of isolated lesions in the epididymis or testis seems indicated.

SUMMARY

Two cases are presented which, so far is as known, are the first to be recorded of isolated metastasis of coccidioidomycosis infection to the genital tract. In one, infection still persists 20 months after epididymo-orchiectomy originally performed for what was considered to be tuberculous epididymitis. In the second case, the genital involvement was localized to the epididymis and testis and was apparently cured by simple epididymo-orchiectomy. The interval between the initial infection and the development of evidence of metastasis in the genital tract was extremely long in both instances.

These cases demonstrate the importance of considering coccidioidomycosis when confronted with a granulomatous lesion of the genital tract, especially in endemic areas, since the condition is so readily mistaken for tuberculosis.

REFERENCES

1. Forbus, W. D., and Bestebreurtje, A. M.: Coccidioidomycosis: A study of 95 cases of the disseminated type with special reference to the pathogenesis of the disease, Military Surgeon, 99:653-719, Nov. 1946.

2. Smith, C. E.: Coccidiosis, coccidioidomycosis (editorial), Radiology, 39:486-487, Oct. 1942.

3. Smith, C. E., Beard, R. R., Whiting, E. G., and Rosenberger, H. G.: Varieties of coccidioidal infection in relation to epidemiology and control of the disease, Am. J. Pub. Health, 36:1394-1402, Dec. 1946.

4. Smith, C. E.: Personal communication.

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EDITORIAL

Professional Incomes

Physicians in all states have recently received a questionnaire from the Office of Business Economics of the U. S. Department of Commerce, asking them to divulge the details of their professional incomes and expenditures. Questions have been raised in some quarters as to the advisability of answering this questionnaire and as to whether or not the statements made by the responding physician will be treated confidentially by government officials.

The answer to such questions could best be stated by saying, "Go ahead, doctor, and answer everything. It's all right."

The Office of Business Economics is an important cog in the commercial statistical division of our government. Its current project of surveying the income of physicians is part of a plan to make such surveys for lawyers, architects, dentists and other professional men, for the purpose of supplying accurate data for the use of professional as well as business and government interests. In this project, the government agency is working with the complete cooperation of the American Medical Association through its Bureau of Medical Economic Research.

Every effort is being made to secure a complete return of the questionnaires, so that a true picture of physicians' incomes may be secured. Both government and A.M.A. experts point to the fact that in previous surveys of this type the income figures have tended to exaggerate the net incomes of physicians because the men in smaller offices, often without adequate secretarial or bookkeeping service, ignored the questionnaires or failed to give information in sufficient detail to enable their returns to be tabulated in computing the average.

To avoid this exaggeration, the government and A.M.A. departments have devised a system of follow-up requests which should produce the needed information and not work a hardship on the physicians making their returns. The system includes a three-way mailing.

The first mailing is going to every other physician on the master file of the American Medical Association, about 100,000 in all. This is a short-form questionnaire which can be handled in a matter of seconds by the physician who has retired, gone out of medical practice or for any reason dropped from the ranks of active practitioners. For those in active practice, the form will require a little longer to complete but will not constitute a real hardship.

A second short-form questionnaire will also go to 10,000 physicians, each of whom will be identified by a code number on the outside of the return envelope. The third mailing will go to 15,000 doctors, also identified by a code number on the return envelope. The code numbers have been placed there for the sole purpose of enabling the surveyors to make follow-up mailings to these smaller lists in an effort to secure a 100 per cent return. Physicians who may be concerned over the presence of a code number may rest assured that once the numbered returns are received, they will be checked off the mailing list and once the return envelopes are opened, the identity of the sender is lost.

Every physician is urged to give this survey his whole-hearted cooperation so that an accurate study may be made. The medical profession is the first of the professional groups of the country to undergo this type of review and it is hoped that it may set a pattern which will encourage other professions to come forward with information which is of vital interest to medicine and government alike.

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NOTICES AND REPORTS

H. Gordon MacLean, President-Elect

The 1950 House of Delegates of the California Medical Association was unanimous in its selection of H. Gordon MacLean of Oakland as President-Elect for 1950-1951. His election to this high post climaxes a career of distinguished service both in professional and in medical organizational fields and comes as testimony of the esteem in which his peers hold him.

Born in Winnipeg, Canada, in 1896, Dr. MacLean received his preliminary education principally in Victoria, British Columbia. His medical degree was received from the Oakland College of Medicine and Surgery in the class of 1917 and he has remained in Oakland in practice since that time.

Dr. MacLean's start in medical practice came in the form of a preceptorship in internal medicine under the late Dr. William H. Streitmann, eminent Oakland internist. His activities were divided between private practice and service in the medical section of the Alameda County Hospital. After four years of preceptorship he became an associate of Dr. Streitmann's and continued in that capacity until the death of the senior physician. Since 1933 Dr. MacLean has been associated with Dr. T. C. McCleave, Jr.

During the course of his practice Dr. MacLean has occupied high offices in some of the leading hospitals in the East Bay area. From 1928 to 1946 he was a member of the medical staff and chief of medical service at Highland Alameda County Hospital and from 1947 to date he has served as consultant in medicine to that institution. He is a member of the attending staff at Merritt Hospital and past chief of the medical department there. He is a member of the active staff of Providence Hospital and for the past ten years has been chief of its medical department.

In community affairs, Dr. MacLean has been unusually active in noteworthy projects. For the past three years he has served as a member of the Institutions Commission of Alameda County, a body of public-spirited citizens which exercises considerable influence in the operation and maintenance of all public institutions in California's third largest county.

In a second field of community affairs, Dr. MacLean has been a director of Hospital Service of California, the northern California Blue Cross plan, since 1937, and has been president of that organization since 1942. In this capacity he has been one of the important leaders in the program of fostering prepaid budget-basis hospital and medical care cost insurance. This experience has been invaluable in the campaigns waged in the past five years by the

C.M.A. and the A.M.A. in fostering voluntary sickness cost insurance programs.

Dr. MacLean has served his county and state medical associations over a long period of years. In 1938 he was elected president of the Alameda County Medical Association and has been active in the policy-making level of that association to this date. In the California Medical Association he has been a member of the Council for four years, chairman of the Committee on Medical Economics for three years, chairman of the Executive Committee, chairman of the Auditing Committee and vice-chairman of the Council. For the past six years he has been a California delegate to the A.M.A. and has served on several committees in the A.M.A. House of Delegates.

Certified in internal medicine in 1937, Dr. MacLean was elected president of the California Society of Internal Medicine in 1949. He is married and the father of two sons.

H. Gordon MacLean has come by his new honor on the basis of his record and his past performance. He has been a willing and active worker at all times and has pledged his continued activities to the work ahead for the next two years. Those who know him know that this pledge will be scrupulously kept. In the field of public relations, in which he has been unusually active and interested, he is expected to provide the kind of leadership that will permit the California Medical Association to maintain its place of high rank among state medical associations.

C. M. A. ANNUAL SESSION 1950

Election of Officers, Councilors and A. M. A. Delegates

OFFICERS

President, Donald Cass, Los Angeles.
President-Elect, H. Gordon MacLean, Oakland.
Speaker, Lewis A. Alesen, Los Angeles, reelected.
Vice-Speaker, Donald A. Charnock, Los Angeles, reelected.

COUNCILORS AT LARGE

(Three-Year Terms)

Sidney J. Shipman, San Francisco, reelected.
Wilbur Bailey, Los Angeles, reelected.
Francis E. West, San Diego, reelected (formerly served as Council appointee to finish term of Walter S. Cherry, Rialto).
Ivan C. Heron, San Francisco, elected to serve remainder of term of H. Gordon MacLean, term expiring in 1951.

DISTRICT COUNCILORS

(Three-Year Terms)

First District, John D. Ball, Santa Ana, reelected.
Fourth District, Neil Dau, Fresno, elected to succeed Axcel E. Anderson, Fresno.
Seventh District, Donald D. Lum, Alameda, reelected.

DELEGATES TO AMERICAN MEDICAL ASSOCIATION

For terms January 1, 1951, to December 31, 1952.

DELEGATES

1. H. Gordon MacLean, Oakland.
2. E. Vincent Askey, Los Angeles.
3. Dwight L. Wilbur, San Francisco.
4. Donald Cass, Los Angeles.
5. Ralph B. Eusden, Long Beach.
6. R. Stanley Kneeshaw, San Jose.

ALTERNATES

1. Leopold S. Fraser, Richmond.
2. H. Clifford Loos, Los Angeles.
3. C. Kelly Canelo, San Jose.
4. L. Duke Mahannah, Long Beach.
5. J. Lafe Ludwig, Los Angeles.
6. Russel V. Lee, Palo Alto.

Names of members of standing committees of the California Medical Association, as appointed by the House of Delegates upon recommendation of the Council, are listed on Advertising page 6 of this issue.

C.M.A. dues for 1951: $40 1951 Annual Session: Los Angeles, May 13-16

In Memoriam

BARROW, WILLIAM HULBERT. Died in San Diego, April 12, 1950, aged 63. Graduate of Harvard Medical School, Boston, 1916. Licensed in California in 1922. Dr. Barrow was a member of the San Diego County Medical Society, the California Medical Association, and a Fellow of the American Medical Association.

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DACOSTA, A. ANTONIO. Died in Spring Valley, April 16, 1950, aged 45. Graduate of Howard University College of Medicine, Washington, D. C., 1931. Licensed in California in 1933. Dr. DaCosta was a member of the San Diego County Medical Society, the California Medical Association, and a Fellow of the American Medical Association.

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MCCARTY, RAY BARDWELL. Died in Riverside, April 15, 1950, aged 50, of acute coronary occlusion. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1899. Licensed in California in 1931. Dr. McCarty was a member of the Riverside County Medical Society, the California Medical Association, and a Fellow of the American Medical Association.

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MCNEILE, OLGA. Died in Los Angeles, April 2, 1950, aged 67. Graduate of the University of California Medical School, Berkeley-San Francisco, 1910. Licensed in California in 1910. Dr. McNeile was a member of the Los Angeles County Medical Association, the California Medical Association, and a Fellow of the American Medical Association.

✤

MONTGOMERY, ROBERT CLYDE. Died in Atwater, January 16, 1950, aged 68, of coronary thrombosis. Graduate of the Bennett College of Eclectic Medicine and Surgery, Chicago, 1911. Licensed in California in 1937. Dr. Montgomery was a member of the Merced County Medical Society, the California Medical Association, and the American Medical Association.

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O'NEILL, BERNARD JOSEPH. Died in San Diego, April 11, 1950, aged 73. Graduate of Rush Medical College, 1908. Licensed in California in 1909. Dr. O'Neill was a member of the San Diego County Medical Society, the California Medical Association, and the American Medical Association.

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POMEROY, FRANK KENNETH. Died in Fresno, April 1, 1950, aged 64, of a heart attack. Graduate of Columbia University College of Physicians and Surgeons, New York, 1914. Licensed in California in 1917. Dr. Pomeroy was a member of the Fresno County Medical Society, the California Medical Association, and the American Medical Association.

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REYNOLDS, EARL OWEN. Died in Los Angeles, March 14, 1950, aged 60, of uremia. Graduate of the University of Louisville School of Medicine, 1914. Licensed in California in 1944. Dr. Reynolds was a member of the Los Angeles County Medical Association, the California Medical Association, and a Fellow of the American Medical Association.

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SHELD-RITCHIE, INER. Died in Riverside, October 24, 1949, aged 65. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1915. Licensed in California in 1915. Dr. Sheld-Ritchie was a member of the Riverside County Medical Society, the California Medical Association, and the American Medical Association.

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VERHALEN, JOHN. Died in the Marshall Islands, April 11, 1950, aged 49. Graduate of Loyola University School of Medicine, Chicago, 1930. Licensed in California in 1944. Dr. Verhalen was a member of the Los Angeles County Medical Association, the California Medical Association, and the American Medical Association.

✤

WALKER, GEORGE ALVIN. Died in San Francisco, April 18, 1950, aged 47, of coronary thrombosis, myocardial infarction. Graduate of the University of Kansas School of Medicine, Lawrence-Kansas City, 1935. Licensed in California in 1948. Dr. Walker was a member of the San Francisco County Medical Society, the California Medical Association, and a Fellow of the American Medical Association.

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WHARTON, JOSEPH EARL. Died in Los Angeles, April 4, 1950, aged 35. Graduate of Ohio State University College of Medicine, Columbus, 1940. Licensed in California in 1947. Dr. Wharton was a member of the Orange County Medical Society, the California Medical Association, and the American Medical Association.

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WATERS, ZURA ORTHELLO. Died in San Francisco, March 10, 1950, aged 60. Graduate of the College of Physicians and Surgeons, Los Angeles, 1918. Licensed in California in 1918. Dr. Waters was a member of the San Francisco County Medical Society, the California Medical Association, and a Fellow of the American Medical Association.

• Questions and Answers about C.P.S. •

Question: **How may I best be assured of prompt payment for treatment of a veteran patient under the C.P.S.-V.A. Home Town Care Program?**

Answer: The best—and only—way to assure your prompt payment for treatment of a veteran is as follows: Within five days of the initial visit submit a Request for Authorization (Form 52) to C.P.S.-V.A. headquarters in San Francisco, Los Angeles or San Diego, depending on your location. When the request has been processed, and if the veteran is eligible for treatment under the Home Town Care Program, you will be sent an Authorization for Treatment (Form 53). At the end of the authorized period (normally a calendar month) return Form 53 to C.P.S.-V.A., showing the authorized services which have been rendered during the period covered by the authorization. Your bill will then be processed by C.P.S.-V.A. and payment will follow.

Many questions of this type can be answered by reference to the C.P.S.-V.A. pamphlet entitled "General Instructions."

Question: **How will the services toward the $5,000 allowable under catastrophic coverage be computed?**

Answer: Payments toward the $5,000 will be based on the current fee schedule paid by California Physicians' Service to member doctors. If the patient's annual gross family income exceeds $3,600 or if services are performed by a non-member physician, the C.P.S. payments will be applied to the physician's usual charge for the services. In such cases, any amount charged directly to the patient by the doctor is not included in the $5,000 liability of C.P.S.

Question: **Under the medical care while hospitalized contract, what medical services are included?**

Answer: Non-surgical professional services, when a registered bed patient in a licensed hospital. That is, services for treatment of such conditions as pneumonia, heart trouble, strokes, etc.

Question: **Is there a limit to the number of times each day the doctor may visit the patient, under the two-visit deductible or the medical care while hospitalized contract?**

Answer: No. There is no limit to the number of necessary visits. The patient, however, pays for the first two in each illness or injury.

Question: **Which C.P.S. members are entitled to laboratory and x-ray services when not hospitalized?**

Answer: With the exception noted below, only those members having two-visit deductible medical benefits or catastrophic coverage are entitled to laboratory and x-ray services when not hospitalized.

The exception is that all C.P.S. members, including those having only surgical-hospital benefits, are entitled to x-rays to determine a possible fracture or dislocation—in case of recent injury or illness—whether they are in or out of the hospital. C.P.S. pays for these x-rays even if they reveal that no fracture or dislocation exists. When billing C.P.S. for such x-rays, doctors should indicate that they were made to determine fracture or dislocation.

Question: **Is it possible for persons to join C.P.S. if they are not members of an employed group of five or more people?**

Answer: Yes. Last year the new individual family plan was made available throughout Northern California to persons not eligible for group enrollment. It has now been extended to Southern California.

Individual family plan memberships provide surgical and hospital benefits for the subscriber and family members alike.

Qualifications for individual C.P.S. membership are easily met. Details are available from any C.P.S. office.

Question: **Are individual family plan members and direct pay members the same?**

Answer: No. "Individual" members are those who join C.P.S. through the individual family plan. "Direct pay" members are those who joined C.P.S. through a group enrollment at their place of employment, but who later left their jobs and continued their C.P.S. membership by making direct dues payments to C.P.S.—instead of paying dues through the group where they joined.

Question: **Does it cost more to continue C.P.S. membership on the direct pay basis than it does as part of a group?**

Answer: Yes, there is a small increase in dues for direct pay members. This increase is necessary because the clerical costs of handling direct payments are greater for C.P.S. than the costs of handling dues paid by an entire group. A further reason, supported by actuarial studies, is that persons who leave the group where they joined C.P.S. often do so for a reason which will be reflected in greater use of their C.P.S. membership. For example, persons who retire from work for reasons of age or health utilize C.P.S. protection more than others.

Question: **What is the catastrophic plan?**

Answer: The catastrophic plan provides protection up to a total of two years or $5,000 against medical and surgical costs of cancer, poliomyelitis, tuberculosis, and 20 other of life's most severe, costly diseases and ailments.

NEWS and NOTES

NATIONAL • STATE • COUNTY

FRESNO

Recommendation that a **pathologist** be engaged by Fresno County for assignment on a part-time basis to the **coroner's office** was forwarded to the board of supervisors last month by the Fresno County Medical Society. It was suggested that the medical examiner be made responsible for determining the cause of death as set down on death reports and that he be available for advice to the coroner in any case in which doubt as to diagnosis might indicate the necessity for autopsy.

LOS ANGELES

The 49th annual meeting of the **American Proctologic Society** will be held in Los Angeles, July 2 to 5, 1950. Information regarding the meeting and the program may be obtained from Wendell Green, M.D., 201 Professional Building, 1838 Parkwood Avenue, Toledo 2, Ohio.

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A **research fund of $3,500** for investigation of diseases of the heart and lungs was presented to the University of California Medical Center, Los Angeles, by the Bay District Surgical Society. The society is made up of a group of Los Angeles, Beverly Hills and Santa Monica surgeons. Members of the staff of the U.C.L.A. Medical School and of the Wadsworth Veterans Administration Hospital will cooperate in the study, which will be concerned primarily with heart disease stemming from rheumatic fever.

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The Los Angeles Obstetrical and Gynecological Society named **Dr. Erle Henriksen,** associate professor of gynecology at the University of Southern California, as **winner of its second annual essay award** for the most outstanding paper on obstetrics and gynecology published during 1949. The winning paper, "The Lymphatic Spread of Carcinoma of the Cervix and of the Body of the Uterus," was published in the *American Journal of Obstetrics and Gynecology,* November 1949.

* * *

A three-day **course in medicolegal problems,** jointly sponsored by the University of California Extension and the School of Medicine and the School of Law, University of California at Los Angeles, is to be given on the U.C.L.A. campus June 19, 20, and 21. Louis J. Regan, M.D., LL.B., professor of legal medicine, College of Medical Evangelists, will be general chairman of the course.

Requests for programs for the course and applications for enrollment may be addressed to S. J. Weinberg, M.D., Head of Postgraduate Instruction, Medical Extension, University of California, Los Angeles 24.

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University of California Extension and the University's School of Medicine have announced a **postgraduate course in diagnosis and therapy of cancer,** including clinical surgery, radiation therapy and endocrine therapy, to be held from July 17 to 22 in the medical library conference room, fourth floor, General Medical and Surgical Hospital, Veterans Administration Center, Los Angeles.

Complete announcement of the course, together with an enrollment blank, may be obtained from the Office of Medical Extension, University Extension, University of California, Los Angeles 24, California. Fee for the course is $100.

SACRAMENTO

The second annual scientific assembly of the **California Academy of General Practice** will be held in Sacramento November 8, 9 and 10, 1950. Attendance of 600 to 700 is expected. Chairman of the committee on local arrangements is Dr. John Rovane of Sacramento, and general chairman of the meeting is Dr. Merlin Newkirk of Los Angeles.

The academy recently announced that Mr. William Rogers, now an employee of Alameda County Medical Association, has been engaged as executive secretary. He will take over his duties with the academy July 1.

SAN DIEGO

Dr. Alvin R. Leonard, formerly of the Bureau of Adult Health, recently accepted appointment as assistant director of the San Diego City-County Health Department, a position which had remained open since July 1949, when Dr. J. B. Askew, then assistant, was appointed health officer upon the retirement of Dr. Alex Lesem.

SAN FRANCISCO

Stanford University School of Medicine has announced 13 **postgraduate courses for practicing physicians** to be held September 11 to 15, 1950. Morning courses, Monday through Friday, 8:30 to noon: (1) general surgery; (2) acute surgical emergencies; (3) surgical anatomy; (4) internal medicine; (5) electrocardiography; (6) diseases of the chest; and (7) pediatrics.

Afternoon courses, Monday through Friday, 1:30 to 5: (8) surgical anatomy; (9) proctology; (10) fundamentals of roentgen diagnosis; (11) fractures; (12) internal medicine; and (13) obstetrics and gynecology.

Fee for two courses (one morning course and one in the afternoon) is $75. Applications and requests for information should be directed to: Dean, Stanford University School of Medicine, 2398 Sacramento Street, San Francisco 15.

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A **postgraduate course in psychiatry and neurology,** to be held at the Langley Porter Clinic, August 28 through November 17, 1950, has been announced by the Extension Division of the University of California School of Medicine. A repetition of a course given previously, it is particularly designed to prepare psychiatrists and neurologists **for taking the examinations of the American Board of Psychiatry and Neurology.** Fee for this course is $200. Further information may be obtained from Stacy R. Mettier, M.D., Head of Postgraduate Instruction, Medical Extension, University of California Medical Center, San Francisco 22, California.

AMERICAN MEDICAL ASSOCIATION

Annual Session

SAN FRANCISCO, JUNE 26-30, 1950

Contemporary Scientific and Social Meetings

A number of scientific organizations and social groups have scheduled meetings in San Francisco during or immediately before or after the A.M.A. Annual Session. A list of announcements of such meetings that have been received by CALIFORNIA MEDICINE follows:

UNIVERSITY OF PENNSYLVANIA ALUMNI SOCIETY DINNER

Fairmont Hotel

June 28, 7 p.m.

Principal Speakers: Dean John McKenney Mitchell, and I. S. Ravdin, John Rea Barton professor of surgery.

Address: Dwight L. Wilbur, M.D., 655 Sutter St., San Francisco.

SOCIETY FOR VASCULAR SURGERY (Scientific Program)

Fairmont Hotel

June 25, morning (9 o'clock) and afternoon (2 o'clock) session. (Meetings open to all physicians).

GEORGE WASHINGTON UNIVERSITY MEDICAL ALUMNI DINNER

Fairmont Hotel

June 29, 7 p.m.

Address: Angelo May, M.D., 450 Sutter St., San Francisco.

A.M.A. GOLF TOURNAMENT

Olympic Golf Club (two courses)

June 26

Address: William J. Burns, Secretary American Medical Golfing Association, 2020 Olds Tower, Lansing 8, Michigan.

PHI BETA PI DINNER

Union League Club, 555 Post St.

June 27, 7 p.m. (Cocktails at 6 p.m.)

Tickets available at a registration desk at A.M.A. convention headquarters.

TUFTS MEDICAL ALUMNI ASSOCIATION DINNER

Rickey's Town House, Van Ness Ave. and Clay St.

June 28, 6:30 p.m.

Tickets: A.M.A. Registration Area 1, or John F. Martin, M.D., 1155 Jones St., San Francisco 9.

1ST MEDICAL REGIMENT REUNION

Claremont Hotel, Berkeley

June 28, 6:30 p.m.; cocktails; 8:00 p.m., dinner ($3.50).

Address: Charles B. Hudson, M.D., 400 29th St., Oakland 9; or Louis B. Goldstein, M.D., 450 Sutter St., San Francisco 8.

AMERICAN COLLEGE OF CHEST PHYSICIANS

St. Francis Hotel

June 22-25

Oral and written examinations for Fellowship will be held June 22. Candidates who would like to take the examination should make arrangements with Murray Kornfield, 500 North Dearborn St., Chicago 10, Illinois.

THE SOCIETY FOR INVESTIGATIVE DERMATOLOGY

Clift Hotel

June 25-26

(See Archives of Dermatology and Syphilology, May 1950, for scientific program).

WESTERN ASSOCIATION OF INDUSTRIAL PHYSICIANS AND SURGEONS

Curran Theater

June 24, 9 a.m. to 5 p.m.

All A.M.A. members invited to attend.

INTERNATIONAL ACADEMY OF PROCTOLOGY

Second Annual Convention (Scientific Program)

June 23-24

Address: Alfred J. Cantor, M.D., 43-55 Kissena Blvd., Flushing, N. Y.

SHASTA

Appointment of **Dr. Byrl Rittenhouse** of Riverside as Tehama County physician, effective July 15, was announced last month by the board of supervisors. Dr. Rittenhouse, who will succeed Dr. Thomas D. Wyatt, now serving on a part-time basis, received the appointment after a letter from the Shasta County Medical Society, pledging support and assistance to him, was read to the county supervisors. In accepting the position, the new county physician said it was with the understanding that the supervisors would favor permitting members of the medical sociey to make the rounds of the hospital.

SOLANO

Dr. H. Gordon MacLean of Oakland, President-elect of the California Medical Association, principal speaker at a meeting of the Solano County Medical Society last month, discussed **"Legislation and Public Relations."**

Other C.M.A. officials at the meeting, which was also attended by guests from the Marin, Napa and Sonoma county medical societies, were Dr. Alson Kilgore of San Francisco; Dr. Dwight H. Murray of Napa, a Trustee of the American Medical Association; Dr. John W. Green of Vallejo, C.M.A. Councilor for the Ninth District; and Dr. F. R. Hook of San Francisco, medical director of the C.M.A. Cancer Commission.

SONOMA

Dr. Robert Westphal, who recently resigned as director of the Riverside County Health Department, was appointed to a similar position in Sonoma County, effective May 1. Dr. Westphal had served in Riverside since June 1948. Before that he was deputy county health officer at Rochester, N. Y.

GENERAL

At the annual meeting of the **California Society of Allergy,** held in San Diego May 1, 1950, the following officers were elected for 1950: President, Frank G. Crandall, Jr., M.D., Los Angeles; president-elect, Samuel H. Hurwitz, M.D., San Francisco; secretary-treasurer, M. Coleman Harris, M.D., Beverly Hills.

* * *

The Foundation of the **American Society of Plastic and Reconstructive Surgery** offers as its **1950 award $500** (first prize of $300, second prize of $200) and a certificate of merit, for essays on some original unpublished subject in plastic surgery.

Competition is limited to residents in plastic surgery of recognized hospitals and to plastic surgeons who have been in such specific practice for not more than five years.

The first prize essay will appear on the program of the forthcoming annual meeting of the American Society of Plastic and Reconstructive Surgery, to be held in Mexico City, November 27 to 29, 1950. Essays must be in before August 15, 1950.

Further details may be obtained from Dr. Clarence R. Straatsma, 66 East 79th Street, New York, N. Y.

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Five California institutions last month received **U. S. Public Health Service grants** totalling $36,518 to aid in laboratory and clinical research on cancer. Two of the grants went to the University of California—$5,298 for studies on the serial passage of Hodgkin's disease extracts in chicken eggs, under the direction of Dr. Warren L. Bostick; $12,000 for isotopic tracer studies of tissue synthesis and the reactions of metabolic antagonists, under the direction of Dr. David Greenberg.

The Laboratory for Research on the Treatment of Cancer, Boulder Creek, was awarded $1,225. Los Angeles County Hospital received $12,500 in support of studies conducted by Dr. Harold F. Pearson on metabolism of tissue in relation to propagation of viruses, and Mount Zion Hospital, San Francisco, was allotted $5,500 for studies by Dr. Gerson R. Biskind on hormone metabolism of experimental ovarian tumors in rats.

BOOK REVIEWS

MORE ABOUT PSYCHIATRY. By Carl Binger, M.D. The University of Chicago Press, Chicago, 1949. $4.00.

The author of this book is associate professor of clinical psychiatry at Cornell University Medical College. A previous volume of his, "The Doctor's Job," won the Norton Medical Award in 1945.

The book is made up of a series of lectures and articles which have been published previously. It is, therefore, a collection of independent essays. The chapters, however, fit in together fairly well, the first four covering problems of psychosomatic medicine followed by a discussion of psychiatric problems and mental health.

The book is designed primarily for popular reading, although the general medical profession will find considerable useful information in it. It is the type of book which a doctor can recommend to a patient who wishes some information along these lines. The chapter on psychoanalysis is a rather good presentation of this subject for those with no knowledge of the subject.

This book, therefore, can be recommended as a good book for popular reading for those who wish further information about psychosomatic medicine and psychiatry.

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QUESTIONS, MEDICAL STATE BOARD, AND ANSWERS. By R. Max Goepp, M.D., Formerly Professor of Clinical Medicine, and Harrison F. Flippin, M.D., Associate Professor of Medicine, both of Graduate School of the University of Pennsylvania. Eighth Edition. W. B. Saunders Company, Philadelphia, 1950. $7.50.

The eighth edition of this old reliable comes after an elapsed period of 11 years since the last edition. It shows evidence of revamping and having been brought up to date in all chapters. A new chapter on psychiatry has been added.

The collaboration of Dr. Harrison F. Flippin, associate professor of medicine, Graduate School of the University of Pennsylvania, has been obtained, along with a staff of qualified editorial consultants.

The subject matter covered is necessarily broad but is done well and adequately. The use of such a volume is admittedly limited but the book accomplishes its purpose very well indeed.

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THE YELLOW EMPEROR'S CLASSIC OF INTERNAL MEDICINE—Chapters 1-34. Translated from the Chinese with an Introductory Study by Ilza Veith, M.A., Ph.D., Lecturer in the History of Medicine, The University of Chicago. The William and Wilkins Company, Baltimore, 1949. $5.00.

How the venerable ancients reached a ripe old age was described by Ch'i Po, physician to the Yellow Emperor, Huang Ti, more than 4,000 years ago: "In ancient times... people . . . understood Tao (and) patterned themselves upon the Yin and the Yang and they lived in harmony with the arts of divination.

"There was temperance in eating and drinking. Their hours of rising and retiring were regular and not disorderly and wild. By these means the ancients kept their bodies united with their souls, so as to fulfill their allotted span completely, measuring unto a hundred years before they passed away."

This, briefly, summarizes much of the medical philosophy expounded throughout the Nei Ching, the Yellow Emperor's Classic of Internal Medicine. And this is the basis of Chinese medicine as it has been practiced through the ages to the present time.

It becomes obvious, immediately, that Chinese medicine is not *scientific* as the Occidental understands the term. It recognizes no accurate anatomy. The chief method of diagnosis is the examination of the pulse. The two methods of healing are the often extremely painful acupuncture and moxibustion. On the other hand, Chinese medicine seeks to prevent illness by setting up a rational system of living. This system depends upon the understanding of Tao, the Right Way. It depends upon acting in accordance with Yin and Yang, the two great principles in nature. And it depends upon the comprehension and practice of numerology. The Nei Ching is the basic textbook of this system. Started perhaps 5,000 years ago, it is a body of folk literature that has grown with time.

In producing this English edition of the Nei Ching, Ilza Veith has performed a difficult feat with distinction. The actual translation takes up only two-thirds of the book. The remainder includes a comprehensive introduction and background explanation of the text. These, along with considerable appendices, help give the reader a basis of understanding for the text proper.

While the reader will not increase his technical knowledge with the Nei Ching, he will find in it rich food for philosophical thought along with some fascinating reading. The publishers have done a fine job of printing on parchment-like paper and have bound the book appropriately in yellow and black.

* * *

STEDMAN'S MEDICAL DICTIONARY — Seventeenth Revised Edition. Edited by Norman Burke Taylor, M.D., The Williams and Wilkins Company, Baltimore, Maryland, 1949. $8.50.

The 17th edition of this scholarly work carries on in the tradition of its predecessors. It is, with certain reservations, an excellent reference on the definitions of medical terms. In order to get the most out of the body of the dictionary, the reader needs to be familiar with some of the appendices, particularly those on medical etymology and the keys to pronunciation and abbreviations.

The reviewer disagrees with the "ivory tower" attitude of the editors in regard to the omission and deletion of trade names. A medical dictionary, by its very nature, must be a complete book of information. The student must be able to find in it anything he needs pertaining to medical words. Whether one approves or disapproves of pharmaceutical and other trade names, they are with us and their existence may as well be acknowledged. Indeed, if the dictionary is not the right book to identify them, what is? (It is noted that the editors have made certain exceptions for trade names which have been accepted in general literature, e.g., adrenalin. Why not include all such words in a separate section?)

* * *

DISEASES OF THE AORTA—Diagnosis and Treatment. By Nathaniel E. Reich, M.D., Associate in Medicine, Long Island College of Medicine. The Macmillan Company, New York, 1949. $7.50.

This is a remarkably complete book for its size and discusses diseases of the aorta from the embryologic, clinical, and radiologic aspects. Each abnormality is clearly illustrated with line drawings and with angiocardiograms. The diagnosis of each lesion is tabulated in simple fashion for ease of reference.

The author has several unusual chapters on diagnostic procedures not requiring radiologic equipment, as well as a chapter discussing angiocardiography, kymography, abdominal arteriography, electrokymography and cardiac catheterization. There is a short chapter on antibiotics and one on

anticoagulants; neither seems to be pertinent to the text, but both are useful adjuncts.

Each chapter has a complete bibliography which adds considerably to the value of the book.

The variety of subjects discussed necessitates a rather brief discussion of each one, but the author has succeeded rather well in emphasizing the important phases of each subject.

The radiologic illustrations are very good; the only suggestion for future editions would be to increase the size of the figures for clarity.

This comprehensive monograph should be well received by the physician interested in diseases of the aorta.

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TUBERCULOSIS—A Global Study in Social Pathology. John B. McDougall, C.B.E., M.D., F.R.C.P. (Edin.), Section of Tuberculosis, World Health Organization. The Williams and Wilkins Company, Baltimore, 1949. $6.00.

The subtitle of this volume indicates the scope of the problem considered. The author's position with W.H.O. (United Nations) places him in a unique position to speak with authority. The first one-third of the book consists of statistical information and comments on the tuberculosis problem of each nation on the earth arranged in alphabetical order. Such information is not available elsewhere to the knowledge of the reviewer and makes this an important source book of information.

The next part contains a summary of prevailing views as to the various factors relating to morbidity and mortality from tuberculosis dealing particularly with sociologic, economic and racial factors.

The third part of the book includes detailed recommendations for the investigation of the tuberculosis problem in a community. Well planned and very specific recommendations are made for the organization of tuberculosis services under varying conditions.

The data presented make it quite clear that the methods utilized in the United States for the prevention and treatment of tuberculosis are not widely applicable to many population groups in other countries. Vaccination with BCG is regarded by the author as the most fruitful approach to the problems of tuberculosis which exist in many nations.

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NORMAL VALUES IN CLINICAL MEDICINE. By F. William Sunderman, M.D., Ph.D., Professor of Experimental Medicine and Clinical Pathology, University of Texas Postgraduate School of Medicine; and Frederick Boerner, V.M.D., Late Associate Professor of Clinical Bacteriology, Graduate School of Medicine, University of Pennsylvania. W. B. Saunders Company, Philadelphia, 1949. $14.00.

In this volume, the authors have done a remarkable job of compilation and sorting, and they have done it with considerable discrimination. They have presented as much data as they could assemble on normal values for all the different systems and regions of the body. They have also collected data on such miscellaneous odds and ends as statistical methods, food values, drugs and doses, isotopes, life and actuarial tables, and tables of weights, measures and standards. In fact, in this book one can find normal values for anything from the reticulocyte count of a healthy man at different altitudes to the number of chews in a standard meal.

With such a tremendous number and variety of values and with the necessary bibliography involved, criteria are sometimes difficult to establish. The reader may not agree with a fair amount of the work quoted, but he must understand that the authors had to start and to stop somewhere in choosing material. And one is bound to note discrepancies: In discussing the normal heart rate (page 5), after mentioning that it is subject to wide physiological variation, the statement is made, "at rest the heart averages 70 to 72 beats per minute." Then, a few lines later, the rate is given as 70 to 75 beats per minute. Differences also occur from page to page in the values given for the chemical compouents of the blood. Furthermore, many tests are simply mentioned by title and not elaborated upon, which is unfortunate. It does the reader little good, for instance, to read only that the "Schneider Index is an exercise tolerance, test that has a rather complex method of scoring and is based upon the differences in heart rate and blood pressure measurement after change of body position and after exercise."

The book is most valuable in giving specific values, especially in tables, for different parts of the body for both adults and children of different ages. In one important aspect of normal values, it does not help the reader: It does not answer the question of how much deviation from the normal is likely to mean abnormality enough to connote disease. However, another book as large as this volume would be necessary to provide that answer.

Whether or not one approves of the criteria, of the individual quotations, or of the discrimination in evaluating the work quoted, one must concede that in this book the authors have produced a reference of unique value. It is to be recommended for every medical library.

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PHYSIOLOGY OF HEAT REGULATION AND THE SCIENCE OF CLOTHING. Prepared at the Request of the Division of Medical Sciences, National Research Council. Edited by L. H. Newburgh, M.D., Professor of Clinical Investigation, The Medical School, University of Michigan. W. B. Saunders Company, Philadelphia, 1949. $7.50.

The editor has collected a remarkable group of essays on a very important subject and one which commands the respect of every physiologist and should capture the interest of every physician. In this volume appears the simple expression of the mechanism of maintaining constant temperature in the human economy, with the most detailed elaboration of the complicated mechanisms which are responsible for maintaining this equilibrium at the extremes of temperature and humidity. The physiologic exchanges of heat loss and production are given both from the biologic and thermodynamic viewpoints. The mechanisms of conduction, radiation, convection and evaporation in maintaining temperature equilibrium are described and expressed in masterful fashion. The first chapter on adaptation to climatic environment is written by F. R. Wulsin, and constitutes a small monograph on an important socio-anthropological study of various peoples of the world exposed to the extremes of temperature; it provides an excellent discussion of human compensations and adaptations to the environment. Aside from the information contained in the monograph, it is delightful reading.

On the whole, the book attempts to describe the marvels of the heat regulation mechanism under the entire range of climatic conditions encountered by the human subject on the earth's surface. Emphasis is placed on the capacity of the mechanisms which are devised to preserve life under the most adverse conditions.

The last third of the volume deals with the topic of the thermobarrier of clothing, which introduces a most detailed and objective study of fabrics and the application of field studies to determine their efficiency, as well as the homeothermic mechanisms of the human body in the desert, the tropics, dry cold climates, wet cold climates, and under circumstances of immersion. It is a highly technical volume, and one which will stand as authoritative for many years to come. It is highly recommended as the final word on the physiology of heat regulation.

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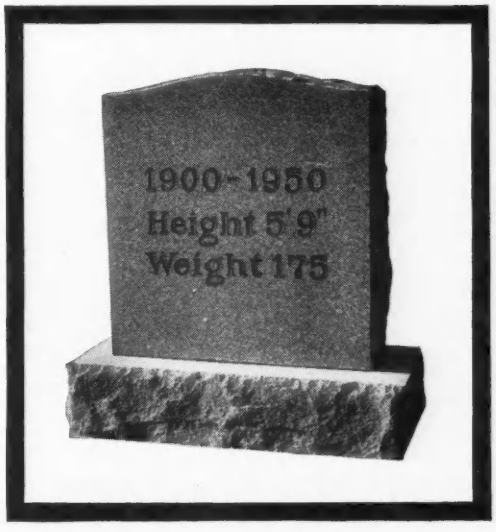

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